Comparative Safety and Survival Rate of Dolutegravir with Efavirenz Based Antiretroviral Therapies for First-line HIV Treatment among HIV Patients in Amhara region, Ethiopia: Retrospective Cohort Study

Melese Alemnew (B.Pharm)

A Thesis Submitted to College of Health Sciences, School of Pharmacy Addis Ababa University in Partial Fulfillment of the Requirements for the Degree Master of Science in Pharmacy Practice (Mpharm)

February, 2022

Addis Ababa, Ethiopia

Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Melese Alemnew, entitled with "Comparative Safety and Survival Rate of Dolutegravir with Efavirenz Based Antiretroviral Therapies for First-line HIV Treatment among HIV Patients in Amhara region, Ethiopia: Retrospective Cohort Study" and submitted in partial fulfillment of the requirements for Degree of Master of Sciences in Pharmacy Practice complies with the regulation of the university and meets the accepted standards with respect to originality and quality.

Internal Examiner: Tamrat Assefa (MSc. Assistant professor)

_____ _____

Signature Date

External Examiner: Ousman Abubeker (MSc. Assistant professor)

_____ _____

Signature Date

Research Advisors: Alemseged Beyene (B.Pharm, MSc Assistant Professor)

_____ _____

Signature Date

Chair of Department or Graduate program coordinator

STATEMENT OF DECLARATION

By my signature below, I declare and affirm that this thesis is my own original work in partial fulfillment of the requirements for the degree of master in Pharmacy Practice

I have followed all ethical principles of scholarship in the preparation, data collection, data analysis and completion of this thesis. All the sources of the materials used for this thesis and all people and institutions who gave support for this work are fully acknowledged. I affirm that I have cited and referenced all sources used in this document. Every effort has been made to avoid plagiarism in the preparation of this thesis. Brief quotations from this thesis may be used without special permission provided that accurate and complete acknowledgement of the source is made. Requests for permission for extended quotations from, or reproduction of, this thesis in whole or in part may be granted by the Head of the Department or all advisers of the theses when in his or her judgment the proposed use of the material is in the interest of scholarship and publication. In all other instances, however, permission must be obtained from the author of the thesis.

Student:

Melese Alemnew Signature: _____ Date: _____

Research Advisor:

Alemseged Beyene (B.Pharm, MSc Assistant Professor) _____ _____

Signature Date

Comparative Safety and Survival Rate of Dolutegravir with Efavirenz Based Antiretroviral Therapies for First-line HIV Treatment among HIV Patients in Amhara, Ethiopia: Region Wise Retrospective Cohort Study

Advisor:

Alemseged Beyene (B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

February, 2022

Addis Ababa, Ethiopia

Addis Ababa University

College of Health Science

Department of Pharmacology and Clinical Pharmacy of Science Research Thesis Submission Form

Name of investigator	Melese Alemnew
Name of advisors	Alemseged Beyene (B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)
Full title of the research	Comparative Safety and Survival Rate of Dolutegravir with Efavirenz Based Antiretroviral Therapies for First-line HIV Treatment among HIV Patients in Amhara region, Ethiopia, 2021.
Duration of study	September 15-2020 to November 7-2021
Study site	Amhara region, Ethiopia
Total cost of the study	28,323.20 ETB
Address of investigator	Mob : +251918253356 Email: melesealemnew2@gmail.com

February, 2022

Addis Ababa Ethiopia

Advisor:

Alemseged Beyene (B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

Acknowledgement

My sincere gratitude goes to God with his Mam St. Mary for his favor and guidance throughout the entire Master's program. I am indebted to the Addis Ababa University for giving this chance to do the study with full budget and Amhara Regional Health Bureau for my educational sponsorship. My honest appreciation goes to my teacher and advisor Alemseged Beyene (B.Pharm, MSc, Assistance Professor of Clinical Pharmacy) for all his valuable comments and advice. Finally, I would like to thank my friends for their technical support.

Abstract

Background: In combination with other two antiretroviral drugs, Efavirenz (EFV) was the treatment of choice for human immunodeficiency virus (HIV) infection. Given concerns about safety and resistance, dolutegravir (DTG)-based regimen have been considered as preferred first-line treatments for both treatment naive and treatment experienced HIV patents.

Objective: To determine the safety and survival rate of DTG compared with EFV-based antiretroviral therapies as first-line HIV treatment among HIV patients.

Methods: A retrospective hospital-based cohort study carried out from September 1, 2019 to August 30, 2020 at HIV clinics of three selected hospitals with HIV treatment centers in Amhara region, Ethiopia. All HIV patients ≥3 years old, those had been either on DTG or EFV-based combination anti-retroviral therapy (cART), and had detectable VL were included. All HIV patients who fulfill inclusion criteria were studied. Data was extracted from patient chart using structure questionnaire. Descriptive statistics, chi-square test, univariate and multivariate cox-regression were performed for data analysis. A statistical significance was considered at p-value ≤ 0.05.

Result: Overall, 990 HIV patients were included in the analysis of which 694 took DTG and 296 received EFV based-regimen. A viral load of < 50 copies/mL was observed in 479 of 694 participants (69%) in the DTG group and 196 of 296 participants (66%) in the EFV group (AHR=1.28, 95%CI: 1.08-1.51; p=0.004).Among patients with a baseline viral load of ≥1000 copies/ mL, a total of 66 from 174 participants (38.0%) in the DTG group and 35 out of 96 participants (36.5%) in the EFV group had a viral load of <50 copies/mL (AHR=0.45, 95%CI: 0.37-0.56; p<0.001). Eleven (1.6%) patients in the DTG group and 8 (2.7%) patients in the EFV group showed virologic failure (p=0.241).Out of the total, 289 (42%) of patients in the DTG group reported adverse drug event (ADE) compared with 147 (50%) in the EFV group (p=0.020).Younger age, opportunistic infections (OI), bedridden condition, no prophylaxis for OI, low baseline cluster differentiation (CD4), high baseline viral load, poor adherence and ADE were predictors of poor survival and also younger age, OI, low baseline CD4, DTG-based initial regimen, poor adherence for cART, naïve treatment history and student job type were predictor of poor safety outcomes.

Conclusions: DTG-based regimen demonstrates improved survival rate and good safety profile than EFV-based regimen for the treatment of HIV infected patients. Baseline CD4+ T-cell count < 200 cells/mm^3, opportunistic infections and poor adherence were factors associated with poor survival outcome and safety outcomes. HIV patients with these risk factors should be treated and monitored regularly.

Keywords: Dolutegravir, Efavirenz, Human immunodeficiency virus, Safety, Survival.

Table of content

Contents **Page no.**

Acknowledgement..... I
Abstract..... II
Table of content..... III
List of acronyms/abbreviations..... V
List of tables..... IX
List of figures..... X
1. Introduction..... - 1 -
1.1. Background..... - 1 -
1.2. Statement of the problem..... - 3 -
1.3. Significance of the study..... - 5 -
2. Literature review..... - 6 -
3. Objective of the study..... - 11 -
3.1. General objective..... - 11 -
3.2. Specific objectives..... - 11 -
4. Methodology..... - 12 -
4.1. Study areas..... - 12 -
4.2. Study design and period..... - 12 -
4.3. Population..... - 12 -
4.3.1. Source population..... - 12 -
4.3.2. Study population..... - 13 -
4.4. Inclusion and exclusion criteria..... - 13 -
4.4.1. Inclusion criteria..... - 13 -
4.4.2. Exclusion criteria..... - 13 -
4.5. Sampling..... - 13 -
4.5.1. Sample size determination..... - 13 -
4.6. Study variables..... - 14 -
4.6.1. Dependent variables..... - 14 -
4.6.2. Independent variables..... - 14 -

4.7. Data collection and management..... - 15 -
4.7.1. Data collection instrument..... - 15 -
4.7.2. Data collectors..... - 15 -
4.7.3. Data quality assurance..... - 15 -
4.7.4. Data analysis and interpretation..... - 15 -
4.8. Ethical considerations..... - 16 -
4.9. Operational definitions and definition of terms..... - 16 -
4.10. Dissemination of findings..... - 17 -
5. Results..... - 17 -
6. Discussion..... - 34 -
7. Conclusion..... - 40 -
8. Recommendation..... - 41 -
References..... - 42 -
Annexes..... - 50 -
Annex I: Treatment staff information sheet..... - 50 -
Annex II: Data collectors..... - 51 -
Annex III: Data abstraction formats..... - 51 -

List of acronyms/abbreviations

ABC	Abacavir
ADE	Adverse drug event
AIDS	Acquired immune deficiency syndrome
cART	Combination antiretroviral therapy
CD4	Cluster differentiation
CNS	Central nervous system
DRH	Debretabor Referral Hospital
DSH	Dessie Specialized Hospital
DTG	Dolutegravir
EFV	Efavirenz
FDA	Food and drug administration
FHCSH	Felege Hiwot Comprehensive Specialized Hospital
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
IQR	Interquartile range
INSTI	Integrase strand transfer inhibitor
NNRTI	Non-nucleoside reverses transcriptase inhibitors
NRTI	Nucleoside reverses transcriptase inhibitors
PIs	Protease inhibitors
RNA	Ribonucleic acid
SPSS	Statistical package for social science
TB	Tubercle bacillus
TDF	Tenofovir
VL	Viral loads
3TC	Lamivudine
WHO	World Health Organization

List of tables

Table 1: Socio-demographic and clinical characteristics of HIV treated patients with DTG and EFV-based cART regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990)..... - 18 -

Table 2: Kaplan-Meier analysis of good survival outcome[◊] and factors associated for DTG compared to EFV-based regimen among HIV patients in DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 01, 2019 to August 30, 2020 (n = 990)..... - 23 -

Table 3: The frequencies of adverse drug events experienced by HIV patients treated with DTG or EFV-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 1, 2019 to August 30, 2020 (n = 990)..... - 26 -

Table 4: Bivariate and multivariate cox-regression analysis of predictors associated with viral load reduction of ≥50 copies/mL among HIV treated patients with DTG compared to EFV-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 01, 2019 to August 30, 2020 (n = 990)..... - 28 -

Table 5: Bivariate and multivariate cox-regression analysis of predictors associated with the occurrence of adverse drug event among HIV treated patients with EFV compared to DTG-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990)..... - 32 -

List of figures

Figure 1: Conceptual framework that shows the association of dependent and independent variables during HIV treatment at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990)..... - 10 -

Figure 2: Schematic presentation of sampling procedure and technique in the evaluation of survival rate and safety outcome of DTG and EFV-based cART regimen among HIV treated patients at DSH, DRH and FHCSH, North West-East, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990)..... - 14 -

Figure 3: Proportion of patients with viral load <50copies/mL and <200copies/mL at final measurement. Kaplan-Meier plots of time from baseline to the final HIV viral load measurement value of (A) <50 copies/mL and (B) <200 copies/mL at FHCSH, DRH and DSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990)..... - 22 -

1. Introduction

1.1. Background

Acquired immunodeficiency syndrome (AIDS) is a human infectious disease with no cure**.** It is a stage of infection where advanced immunosuppression, progressive clinical deterioration, and opportunistic infections (OI) occur. It leads a fatal infection if left untreated with effective and safe medications (Paul E. Sax, 2017, Lu et al., 2013).

According to global AIDS update in 2020, out of 37.7 million people living with Human Immunodeficiency Virus (HIV) 27.5 million (72.9%) were accessing combination antiretroviral therapy (cART) which is 1.5 times greater than 2015 reports; 17.1 million (49.4%) out of 34.6 million HIV patients were on antiretroviral therapy (UNAIDS, 2021).

Even no curative medications available, thanks for cART, fewer people were dying of HIV related causes: 680000 deaths registered in 2020 down 77% from 2003 (3 million), the date that treatment targets were first established (WHO, 2020).

Treatment with cART and prophylaxis for common OI improved clinical condition of patient and decreased complications of the disease (Paul E. Sax, 2017). Starting cART in asymptomatic patients relatively at high cluster differentiation (CD4) cell counts is more effective to reduce viral load, prevent immunodeficiency, delay time to onset of AIDS, reduce non-AIDS morbidity, and decrease risk of drug toxicity, viral transmission, and selecting resistant virus (Paul E. Sax, 2014).

An ideal antiretroviral drug is expected to have long term efficacy, long term tolerability, minimal drug-drug interaction, no food or timing restrictions and barrier to viral resistance (Alice K. Pau, 2018). Moreover, an initial cART regimen selection is determined based on the drug's safety, adherence of patient, food requirements, drug interactions, degree of resistance and comorbid conditions (Jason J. Schafer, 2018).

The efficacy and safety of cART has largely improved with the arrival of newer antiretroviral drug classes (Kanters et al., 2016). Novel, convenient, actually more safe

and suitable HIV drugs have been developed through synthetic modification and new synthesis (FMoH, 2019, Fantauzzi et al., 2013).

Dolutegravir (DTG)is the most widely used integrase strand transfer inhibitor (INSTI) by developing countries for HIV infected patients followed its approval in 2013 (Rutter, 2018). It is the most recent United States Food and Drug Administration (FDA) approved and potent drug of the INSTI. It is a once-daily, pharmacokineticaly unboosted second-generation INSTI that is effective as first-line antiretroviral therapy for HIV positive individuals along with either Abacavir/Lamivudine (ABC/3TC) or Tenofovir/Emtricitabine (TDF/FTC) (Raffi et al., 2015, Kandel and Walmsley, 2015, Cruciani and Malena, 2015, Dow and Bartlett, 2014).

According to the 2018 national HIV treatment guidelines of Ethiopia, Efavirenz (EFV)-based regimen considered to be the preferred first-line regimens for women & adolescent girls who have desire for pregnancy or are pregnant and children aged 3 to 10 years old (FMoH, 2018). The use of INSTI, particularly DTG combined with two nucleoside reverse transcriptase inhibitors (NRTIs) has greater efficacy and improved tolerance to EFV-based regimens (Kanters et al., 2016, Sluis-Cremer et al., 2015).

The most unique features of DTG are its once-daily dosing for ART-naive patients, lack of cross resistance to first generation INSTI, high genetic barrier to resistance, and favorable safety profile compared to other non DTG-based regimen (Dow and Bartlett, 2014, Kandel and Walmsley, 2015, Marco Vitoria, 2018, Cruciani and Malena, 2015, Sharon Walmsley, 2015, Dehority et al., 2015). The non-selected DTG for resistance mutations is due to its extended binding time with integrase and higher ability to prevent replication of the viruses (Wainberg, 2014).

With its good efficacy, tolerability, simplicity of dosing and compatibility profile, DTG is assured to be among the preferred drug in the treatment of HIV infection (Cottrell et al., 2013, Cruciani and Malena, 2015, Fantauzzi and Mezzaroma, 2014, Blake Max, 2014, Bruzzese et al., 2018). Its efficacy against treatment of both treatment-naïve and treatment-experienced HIV infected patients reported elsewhere (Cruciani and Malena, 2015, Blake Max, 2014, Mercadel et al., 2014, Fantauzzi et al., 2013). This drug has also

favorable bioavailability data which enables it suitable for once daily dosing, doesn't require a booster and better absorption regardless of food intake (Cruciani and Malena, 2015, Comi and Maggiolo, 2016, Kandel and Walmsley, 2015, Keeshin and Feinberg, 2015, Miller et al., 2015, Taha et al., 2015).

Reduction of pill burden, lack of significant drug interactions, minimal adverse drug event (ADE), and the low risk of drug resistance are the main improvements of DTG-based regimen (Bruzzese et al., 2018, Fourati et al., 2015, Miller et al., 2015).

DTG is convenient for those patients intolerant to other cART and are on other medications for tubercle bacillus (TB), hepatitis C, seizure, or contraception (FMoH, 2019, Osterholzer and Goldman, 2014). Being potent and effective, high level of safety and lower interactions with immunosuppressive agents, low impact on graft function and convenient dosing, DTG satisfies the requirements of treatment for organ transplant recipient HIV infected patients (Fantauzzi et al., 2013).

The generic single-tablet regimen containing TDF/3TC/EFV is still effective and well-tolerated to use it as first-line antiretroviral therapy in resource-limited settings (McLaughlin et al., 2018). Currently EFV-based regimens are a treatment of choice in HIV infected children particularly those required tuberculosis co-treatment (Menéndez-Arias et al., 2020). The Ethiopia national comprehensive guideline recommends DTG-based as a preferred first-line regimen for adults and adolescents, with consistent and reliable contraceptive use for female, and children of ≥ 20kg in weight including those with TB/ HIV- co infection (FMoH, 2018).

1.2. Statement of the problem

The introduction of cART as the standard of care causes a significant reduction in mortality, and morbidity associated with OI but due to uneven accesses of treatment and information, side effects related to cART, lack of long-term efficacy and larger number of pill burden there is a high level of treatment failure (Fantauzzi et al., 2013, Fantauzzi and Mezzaroma, 2014).

Basic researches undertaken to discover a cure for HIV and to develop new drugs or formulations for its prevention but it is still on treating infected patients with limited number of therapy options due to the developed drug resistance and poor safety outcomes (Iyidogan and Anderson, 2014). Drug resistance mutations negatively affect viral load control and durability of cART (Ying Zhou, 2016, Alemseged Abdissa, 2014). As 2016 HIV country profile, 420000 HIV patients received cART and 20000 died due to HIV in Ethiopia. From those patients receiving cART only 51% of them were virally suppressed due to inadequate services, drug resistance and ADE of available cART drugs (UNAIDS/WHO/UNICEF, 2017).

Inadequate coverage and quality of services, inequities among HIV patients, burden of co-infections and other comorbidities, poor adherence and emergence of drug resistance virus were the major challenges in HIV treatment (Organization, 2016, Seyler et al., 2018).

Low quality cART service provided due to the availability of lower performance tests for monitoring clinical and immunological improvement, testing drug resistance and evaluation of therapy outcomes, (Jean Joel R. Bigna, 2016, Misgena, 2011).

A viral load suppression to less than the limit of currently available assay methods impacted with the prevalent of major OI, and both short- and long-term drug side effects. The impact of globalization and co-morbid illness like diabetic mellitus, hypertension and dyslipidemia in Sub Saharan Africa has to be large both in HIV prevalence and its treatment outcome (Young et al., 2009).

The long term effect and role of HIV treatment regimen, including newly introduced regimens like INSTI is not well investigated in Ethiopia HIV infected patients (Valentina Montessori, 2004).

A treatment failure for HIV was high in Ethiopia. A failure for non-nucleoside reverse transcriptase inhibitors (NNRTI) based first-line antiretroviral regimens in Gondar University Teaching Hospital were found to be 4.1% with a significant predictors of poor treatment adherence and low baseline CD4 (Ayalew et al., 2016, Endalamaw et al., 2020, Derseh et al., 2020).

Because of ADE, poorer overall efficacy, ranking of FDA pregnancy category and high level of drug-resistance compared with newer antiretroviral, there is a need to reconsider the role of EFV as first-line cART (Rutstein et al., 2019, Raffi et al., 2014). High prevalence of transmitted NNRTI resistance compromises the success of EFV-based regimens (Rutstein et al., 2019, Tzou et al., 2020).

Efavirenz based treatment regimens were the major causes of HIV drug resistance and patient mortality compared to other cART regimens (Luo et al., 2019, Mendoza et al., 2016, Mziray et al., 2020). Unlike DTG which has higher genetic barrier, only one mutation is enough to bring about high level of resistance in EFV (Ankur Gupta-Wright, 2020).

Moreover, non-adherence that resulted in treatment discontinuation and mortality is highly associated with EFV-based regimen compared to DTG-based regimen (Avert.org, 2019). Considering DTG-based over EFV-based regimen had better health benefits, lower rate of treatment discontinuation and greater viral load reduction (Ankur Gupta-Wright, 2020, Avert.org, 2019).

1.3. Significance of the study

A better understanding of HIV patient's safety and survival rate from the front line available cART drugs enable stakeholders (like health care providers, policymakers, governmental, non-governmental, and private organizations, trainers and individuals involved in HIV patients care) to develop strategies that can improve their HIV service delivery outcome.

Multisite, comprehensive and periodic studies that determine safety and survival rates of HIV treated patients from their cART regimens at some intervals were vital to prevent the incidence of drug resistance, viral load increase, toxic drug effects, and associated complications in our country.

However, limited data were available on the safety and survival rates of HIV patients taking DTG compared EFV-based regimens in Ethiopia. Determination of patient safety and survival rate of HIV patients are important for curbing the problems of treatment failure, improve patient's survival, clinical outcome and quality of life as well as to

preserve long term efficacy of available drugs. Therefore, the aim of this study is to determine the safety and survival rates of DTG compared to EFV-based cART regimen among HIV infected patients in Amhara region, Ethiopia. This study will also provide baseline information to conduct other similar studies on HIV treatment.

2. Literature review

2.1. Comparison of safety and efficacy of antiretroviral regimens

Dolutegravir based cART achieves a greater viral suppression compared with non-DTG containing cART particularly in those with high baseline VL (>100,000 copies/ mL) or ≤ 200 CD4+ T-cells/mm^3 (Cruciani and Parisi, 2019, Snedecor et al., 2019). Response rates to viral loads (VL) of ≤ 50 copies/mL were 90% for DTG and 82% for EFV at week of 48 of a randomized study conducted at 34 sites (Van Lunzen et al., 2012).

According to a multicenter randomized trial conducted in Cameroon, at week 48**,** a VL< 50 copies/mL was achieved 74.5% in the DTG group and 69.0% in the EFV group. Similarly those patients with a baseline VL of ≥100,000 copies/mL, a VL of < 50 copies/mL was observed in 66.2% in the DTG group and in 61.5% in the EFV group. In this study, virologic failure was detected in 3 participants of the DTG group and in 16 participants of the EFV group (Charles Kouanfack, 2019).

Dolutegravir 50 mg containing once daily dosing resulted in significantly higher virologic suppression (HIV ribonucleic acid [RNA] < 50 copies/mL) and increase in CD4+ cells/mm^3 compared with EFV-based once daily dosing (Hans-Ju¨rgen Stellbrink, 2013, Patel et al., 2014). In a randomized, double-blind study, a VL < 50 copies/mL was attend 88% in the DTG–ABC–3TC group and 81% in the EFV–TDF–FTC group at week of 48. The CD4+ T-cell count was also 267 in DTG and 208 cells/mm^3 in EFV group (Walmsley et al., 2013).

The drug resistance mutation in prenatally infected HIV patients was 54.1%, 27.6% and 27.0% for NRTIs, protease inhibitors (PIs) and NNRTIs respectively (M de Mulder, 2014). In related to EFV-based regimens, a significantly greater proportion of cART

starting mothers late in pregnancy attained VL of <50 copies/mL with DTG (Catriona Waitt, 2015).

Dolutegravir had a shorter (28 vs. 84 days) median time to VL suppression when combined with ABC-3TC than TDF-3TC containing NRTI regimen (Walmsley et al., 2013).

In a prospective cohort study conducted on 265 patients at Jimma Ethiopia, virological failure was observed in 5.3% participants where M184V and K103N were the most frequent NRTI and NNRTI mutations respectively (Alemseged Abdissa, 2014).

A significant greater VL suppression < 50 copies/mL was observed in the DTG group (74%) compared with the EFV group (43%) of pregnant mothers but more serious ADE were reported in the DTG group (22%) compared with (11%) the EFV group (Kenneth Kintu, 2020).

In a randomized controlled trial conducted on mothers at post-partum, there was a significantly greater viral load reduction of < 50 copies/mL in DTG-based regimen (69%) compared to EFV-based regimen (38.7%). The median time it took to attain this result was reduced by half of that EFV-based regimen (Catriona Waitt, 2015).

Dolutegravir based regimen showed an improved safety and survival compared with the regimen of EFV-based cART(Walmsley et al., 2013, Sharon Walmsley, 2015). The safety of once daily 50 mg DTG in integrase inhibitor-naive individuals was superior to EFV-based regimens (Curtis L, 2014). DTG with a 3TC (FTC) plus TDF or ABC have similar efficacy in cART naïve HIV patients (Anne Derache, 2019).
Achieving therapeutic concentrations in the CNS, DTG can be an effective regimen in subjects with neurocognitive complications of HIV disease (70). The dose of DTG increased to 50 mg twice-daily when taken with potent uridine diphosphate lucuronosyl transferase 1A or Cytochrome P, 3A inducers or those patients suspected to have INSTI-resistant mutations (Allan R Tenorio, 2019, Song et al., 2014). On the other hand, maximum concentration in HIV patients ≥ 60years old was significantly higher compared younger subjects in DTG-based regimen (Emilie R. Elliot, 2018).

The DTG-based regimens both in cART-naïve and treatment experiencing patients showed that a risk of having treatment limiting rash and neuropsychiatric events significantly lowers than patients on EFV-based regimens (Mondi et al., 2019, Walmsley et al., 2013, Hill et al., 2018). Moreover virologically suppressed EFV-based HIV patients who was experiencing central nervous system (CNS) toxicity results in significant improvements when switched to DTG-based cART(Michael R. Keegan, 2018, Ricky Hsu, 2018).

Compared to EFV, DTG exhibits lower level of viral resistance, concomitant drug interactions and superior survival rate of viral suppression (Comi and Maggiolo, 2016, Walmsley et al., 2013). It is more effective than EFV regarding VL suppression and CD4 proliferation (Raffi et al., 2014, Rutherford and Horvath, 2016). Even the upturned benefit in efficacy related to DTG-based treatment may not be worth the high incremental costs over EFV-based cART(Peng et al., 2014).

The risk of cardiac side effect between DTG and EFV was comparable (Hill et al., 2018). Dolutegravir containing cART showed enhanced lipid lowering effect and can be a preferred option for older patients those are at risk of metabolic syndrome and cardiovascular disease (Bagella et al., 2019, Gatell et al., 2017, Sharon Walmsley, 2015). Lipid and metabolic profile improved in DTG/ABC/3TC treated patients especially in those switched from a boosted protease inhibitor based regimen (Bagella et al., 2019, Romina Quercia, 2015).

The safety of DTG on pregnant mother and her fetus was similar compared to EFV-based cART(Zash et al., 2018). Although neural tube defect risks are higher in DTG than EFV, it leads to fewer deaths among women and overall HIV transmissions (Dugdale et al., 2019). In ART-naive patients a regimen of EFV significantly increased bone turnover markers compared to DTG-based regimen (Tebas et al., 2015).

Although it is less common, hyperglycemia is a potential side effect of DTG (McLaughlin et al., 2018a). Treatment-naïve HIV patients starting DTG-based regimens show significant weight gain than those starting EFV-based regimens (Kassem Bourgi

2019). Headache and insomnia are the most common and frequently reported ADE of DTG (Osterholzer and Goldman, 2014).

Evaluating the high-level efficacy, patient adherence and low level of resistance, DTG is more effective and less costly in the management of treatment naïve and treatment-experienced HIV infected patients when compared to previous first line cART drugs (Amy Zheng, 2018). Dolutegravir based regimen brings HIV patient health benefits and is cost-effective including in women intending pregnancy to use as a preferred cART(Andrew N Phillips, 2020).

2.2. Factors associated with safety and survival rate

It was reported that the new HIV cases in Amhara region from 2015 to 2018 were greater than 57000 in which women and age group of 25-49 comprises more; 59% and 70% respectively. The report showed that the average incidence rate for the four years were 6.9 per 1000 HIV patients and it was higher in Dessie, Bahirdar and Gondar in descending order (Worku et al., 2020).

Inadequate adherence, non-disclosed HIV status, preexisting drug resistance, regimen complexity, side effects, advanced clinical stage and suboptimal pharmacokinetics can lead to patient attrition, persistent viral replication and evolution of drug resistance (Paul E. Sax, 2014, Abebe Moges et al., 2020, Alemseged Abdissa, 2014).

Poor medication adherence is the primary cause of treatment failure which results in sub inhibitory drug levels that allows ongoing viral replication and potentially the emergence of resistant virus (Astuti and Maggiolo, 2014).

Two percent in the DTG group and 10% in EFV-based regimen discontinued therapy owing to ADE (Walmsley et al., 2013). Moderate-or-higher intensity drug-related ADE in the EFV group were 20% while it is 8% in the DTG group (Van Lunzen et al., 2012).

Late presentation for HIV care is responsible for death, immunological failure and discontinuation of treatment in both children and adult patents. Illiterate people, patients

who drink alcohol, smoke tobacco, mentally retarded or ill patients and bed ridden condition had also more likely to go their HIV treatment discontinuation (Mondi, 2019).

Likewise in meta-analysis virologic failure for HIV treatment was shown to be determined by the advanced clinical stage of patient at baseline, presence of OI, and poor adherence for cART (Endalamaw et al., 2020).

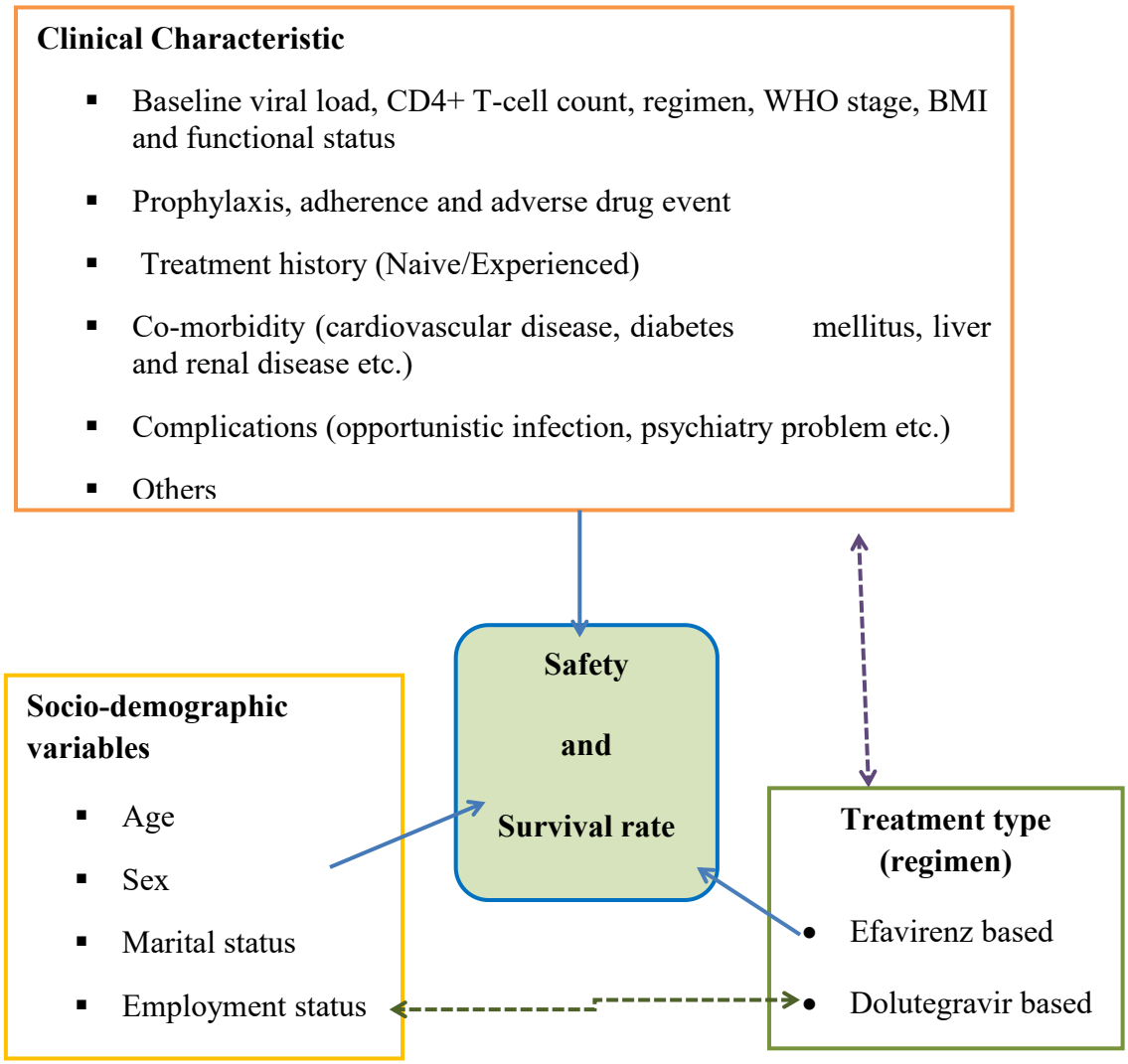

Figure 1: Conceptual framework that shows the association of dependent and independent variables during HIV treatment at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990).

3. Objective of the study

3.1. General objective

The study aimed to compare the safety and survival rate of dolutegravir with efavirenz based regimen for first-line HIV treatment among HIV patients in Amhara reion Ethiopia.

3.2. Specific objectives

- To compare the safety of dolutegravir with efavirenz based regimen among HIV patients
- To compare the survival rate of dolutegravir with efavirenz based regimens among HIV patients
- To determine factors that predicts poor safety outcomes of dolutegravir with efavirenz based regimens among HIV patients
- To determine factors that predict poor survival rate of dolutegravir with efavirenz based regimens among HIV patients

4. Methodology

4.1. Study areas

The study was conducted in three selected hospitals at Dessie Specialized Hospital (DSH), Debretabor Referral Hospital (DRH) and Felege Hiwot Comprehensive Specialized Hospital (FHCSH); Amhara region, Ethiopia HIV treatment centers based on their HIV prevalence.

Debretabor Referral Hospital was established in 1931 G.C in South Gondar Zone, North West Ethiopia. It is 99 kilo meters away from Bahirdar, main city of Amhara region and 667 kilo meters North of Addis Ababa. It has 214 beds and provides both outpatient and in-patient services to a catchment population of more than 2.7 million including HIV. It gives a service for around 1866 HIV patients.

Felege Hiwot Comprehensive Specialized Hospital is founded in 1971 G.C and located in Bahirdar, North-West Ethiopia. It serves for about 10 million catchment population including HIV with 492 beds. Currently it serves for 6635 HIV patient.

Dessie Specialized Hospital was established in 1962 G.C and located in South Wollo Zone, North-East Ethiopia. It is found 397 kilo meters East of Addis Ababa and expected to give a comprehensive service for about 12 million populations with 597 beds. It has 5466 HIV patients currently on treatment.

4.2. Study design and period

Hospital based retrospective cohort study was conducted to collect demographic and clinical data from HIV infected patients' medical record who had a follow up at HIV treatment centers between September 01, 2019 and August 30, 2020.

4.3. Population

4.3.1. Source population

All HIV patients who took antiretroviral therapy at DSH, DRH and FHCSH HIV treatment centers September 01, 2019 and August 30, 2020.

4.3.2. Study population

All HIV patients who took DTG or EFV based first-line antiretroviral therapy; fulfill the inclusion criteria and having a follow up during the study period.

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

All HIV patients with detectable VL, age ≥3 years old and had been either on DTG or EFV-based cART regimen.

4.4.2. Exclusion criteria

HIV patients who had incomplete data and those transferred out to other treatment centers for follow up were excluded.

4.5. Sampling

4.5.1. Sample size determination

All HIV patients in the three hospitals who fulfill the inclusion criteria were taken as a sample to get large sample size and increased statistical power of the study. From a total of 13,967 HIV patients (1,866 from DRH, 5,466 from DSH and 6,635 from FHCSH) 9,899 of them took either DTG or EFV-based regimen. Out of this 1,057 patients had detectable viral load within the study period. Then after excluding died (17) and lost to follow-up (50), 990 participants (273 from DRH, 350 from DSH and 367 from FHCSH) were remained to be studied. All study population who fulfill inclusion criteria were sorted out along with their medical record number using treatment software in each respective hospital. Based on their medical record number, treatment charts of those patients were accessed to be reviewed.

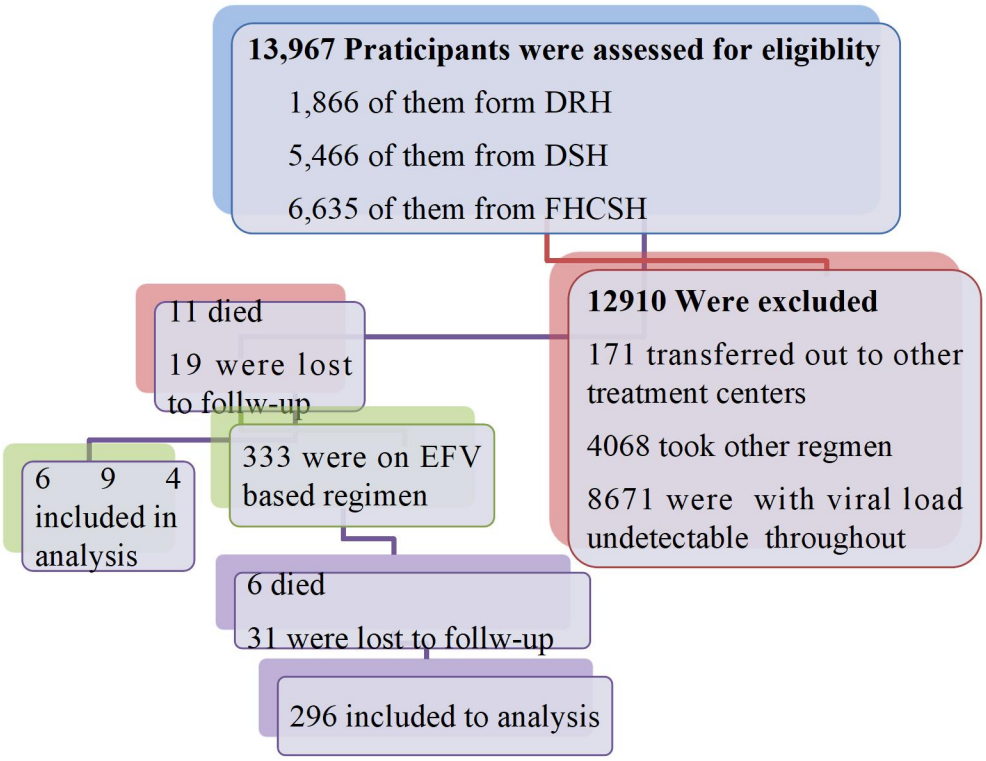

Figure 2: Schematic presentation of sampling procedure and technique in the evaluation of survival rate and safety outcome of DTG and EFV-based cART regimen among HIV treated patients at DSH, DRH and FHCSH, North West-East, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990).

4.6. Study variables

4.6.1. Dependent variables

Safety and survival rate of HIV patients

4.6.2. Independent variables

Socio-demographic variables (age, sex, and employment status), clinical characteristic (baseline viral load, baseline CD4+ T-cell count, WHO stage, body mass index, treatment history, comorbid condition, complications, functional status, prophylaxis, adherence and adverse drug event and treatment type at baseline [EFV or DTG based]).

4.7. Data collection and management

4.7.1. Data collection instrument

After reviewing different published articles, treatment entry and follow-up forms, patient registers and laboratory requests a data extraction tool was prepared and used to collect demographic, clinical, immunological, and laboratory data. Since it was secondary data, only the English version of the tool was used.

4.7.2. Data collectors

Two pharmacists and four BSc clinical nurses were recruited as data collector by providing training about data collection procedure from patient charts using a structure questionnaire. Data collectors and principal investigator undertook all necessary preventive actions of Corona virus disease in 2019. The trained data collectors extracted socio-demographic characteristics as well as clinical data on safety and survival from patient chart using structured questionnaires. The principal investigator supervises the overall data collection process and check daily basis about the data completeness.

4.7.3. Data quality assurance

To assure the quality of data, the structured questionnaire was designed after reviewed various literatures. Data collectors were trained to create a common understanding of how to collect the data and to familiarize the data extraction checklist. Validity and reliability of the instrument was tested on 5% of the total sample size outside of the study site before actual data collection time. The principal investigator supervises data collectors and cross checked information on clinical evaluations and laboratory result with collected data daily to check for completeness, accuracy, clarity, and consistency. Any error or doubt and incompleteness were corrected accordingly. The data was cleaned up rigorously before its analysis.

4.7.4. Data analysis and interpretation

The data were entered and analyzed using Statistical Package for Social Science (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study

participants. Tables and charts were used to present statistically and/or clinically significant results. After checking the proportional hazard assumption using log minus log graph and time dependent cox model, variables in bivariate analysis with *p*-value ≤ 0.2 were further analyzed in multivariate cox-regression to control the effect of confounders. Survival rates in month using the time interval between the dates of viral load measurement were estimated by Kaplan-Meier and differences in survival rates were tested by the log-rank statistic.

4.8. Ethical considerations

The ethical approval and clearance was obtained from the Ethics Review Committee of the School of Pharmacy, College of Health Sciences; Addis Ababa University through a letter reference number of ERB/SOP/202/09/2020. Being secondary data; it was difficult to assure informed and written consent from the patients, so that permission was secured from each hospital's quality assurance department and HIV focal person to access patient's data. The privacy of personal information was strictly preserved.

4.9. Operational definitions and definition of terms

Preferred Regimens: Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile and ease of use (Paul E. Sax, 2017).

Antiretroviral treatment failure: Either of virologic, immunologic or clinical failure

Virologic failure: Inability to achieve virologic suppression, or occurrence of virologic rebound or plasma viral load above 1000 copies/mL based on two consecutive viral load measurements after 3 months, with adherence support (FMoH, 2018) .

Immunologic failure: CD4 count falls to the baseline (or below) or persistent CD4 levels below 100 cells/ mm^3 for patients older than 5 years and persistent CD4 levels below 100 cells/mm^3 (FMoH, 2018).

Clinical failure: Occurrence or recurrence of HIV-related events after at least 3 months on potent antiretroviral therapy (FMoH, 2018).

Survival rate: The percentage of people or treatment group who reduced VL or increased CD4 for a certain period of time after they start treatment of HIV.

Safety: The prevention of errors and adverse effects to patients associated with medication use.

Complications: Occurrence of severe opportunistic infections as a result of suppression of T cell-mediated immunity (such as cardiopulmonary complications, central nervous system complications and tumors).

Undetectable viral load: When the viral concentration in blood is < 50 copies/mL.

Good adherence: If the percentage of missed dose is ≥95% (<2 doses out of 30 doses or <3 doses out of 60 doses) as documented by physician (FMoH, 2018).

Fair adherence: If the percentage of missed dose is 85-94% (3-5 doses out of 30 doses or 3-9 doses out of 60 doses) as documented by physician (FMoH, 2018).

Poor adherence: If the percentage of missed dose is <85% (>6 doses out of 30 doses or >9 doses out of 60 doses) as documented by physician (FMoH, 2018).

Ambulatory: Able to perform activity of daily living, not able to work (Abuto et al., 2021).

Bedridden: A patient unable to perform routine activities of daily living (Abuto et al., 2021).

Working: Able to perform routine activities of daily living inside or outside the home (Abuto et al., 2021).

Lost to follow up: A patient interrupt treatment care for 1-3 months after the last appointment (Abuto et al., 2021).

4.10. Dissemination of findings

The result will be disseminated to Amhara regional health bureau, College of Health Sciences, Addis Ababa University, for each respective study site and other HIV coordinating organizations. Moreover, the findings will be presented in local and international scientific conferences, and published in a reputable journal.

5. Results

Out of 990 total study participants, 694 (70%) of them were taking DTG-based regimen whereas 296 (30%) of them received EFV-based regimen Figure 2. Demographic and clinical characteristics of patients at baseline were plausibly selected between the two treatment groups. The proportion of patients being female, initial viral load≥1000 copies/mL, baseline CD4+ T-cell count <200 cells/mm^3, bed ridden functional status,

treatment duration and young median age was higher in EFV-based compared to DTG-based regimen Table 1.

More than half (55%) of the participants were females. The mean (SD) age of the participants was 38 (± 13) years. Seventy eight (8%) HIV patients were widowed while 108 (11%) were divorced. Regarding the family planning method, 512 (52%) of the study participants was used condom and 193 (20%) was on abstinence method. Out of 541 female participants, 64 (12%) and 60 (11%) were pregnant and breast feeding, respectively of which 104 (11%) of HIV patients were treatment naive. The median baseline viral load was 455 copies/mL and 270 (27%) of the participants had a baseline viral load of ≥1000 copies/mL. The median CD4+ T-cell count was 235 cells/mm^3; and 722 (73%) and 375 (38%) of participants had a baseline CD4+ T-cell count of less than 350 and 200 cells/mm^3 respectively. In the study period 831 (95%) of the study participants were started with TDF than zidovudine or ABC plus 3TC in both regimen groups.

Table 1: Socio-demographic and clinical characteristics of HIV treated patients with DTG and EFV-based cART regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990).

Socio-demographic characteristics		DTG Group - no. (%) (n = 694)	EFV Group - no. (%) (n =296)	Total participants - no. (%) (n = 990)
Treatment site	Felege Hiwot CSH	261 (37.6)	106 (35.8)	367 (37.1)
	Dessie Specialized Hospital	249 (35.9)	101 (34.1)	350 (35.4)
	Debretabor Referral Hospital	184 (26.5)	89 (30.1)	273 (27.6)
Age (years)	<15	10 (1.4)	40 (13.5)	50 (5.1)
	15-24	49 (7.1)	22 (7.4)	71 (7.2)
	25-34	145 (20.9)	86 (29.1)	231 (23.3)
	35-44	248 (35.7)	110 (37.2)	358 (36.2)
	≥45	242 (34.9)	38 (12.8)	280 (28.3)
Sex	Male	370 (53.3)	79 (26.7)	449 (45.4)
	Female	324 (46.7)	217 (73.3)	541 (54.6)
Marital status	Single	73 (10.5)	49 (16.6)	122 (12.3)
	Married	455 (65.6)	227 (76.7)	682 (68.9)

	Divorced	94 (13.5)	14 (4.7)	108 (10.9)
	Widowed	72 (10.4)	6 (2.0)	78 (7.9)
Job type	Un-employed	25 (3.6)	8 (2.7)	33 (3.3)
	Student	46 (6.6)	40 (13.5)	86 (8.7)
	Others	425 (61.2)	162 (54.7)	587 (59.3)
	Employed	198 (28.5)	86 (29.1)	284 (28.7)
Baseline regimen	DTG	80 (11.5)	286 (96.6)	366 (40.0)
	EFV	614 (88.5)	10 (3.4)	624 (63.0)
Body mass index	18.5-24.5	626 (90.2)	265 (89.5)	891 (90)
	>24.5	6 (0.9)	6 (2.0)	12 (1.2)
	<18.5	62 (8.9)	25 (8.4)	87 (8.8)
Presence of OI	Yes	52 (7.5)	26 (8.8)	78 (7.9)
	No	642 (92.5)	270 (91.2)	912 (92.1)
Prophylaxis for OI	Yes	353 (50.9)	121 (40.9)	474 (47.9)
	No	341 (49.1)	175 (59)	516 (52.1)
Family planning method	Not using any contraceptive	80 (11.5)	103 (34.8)	183 (18.5)
	Condom	386 (55.6)	126 (42.6)	512 (51.7)
	Oral contraceptive	23 (7.1)	20 (9.2)	43 (7.9)
	Injectable/Implant	39 (12.0)	20 (9.2)	59 (10.9)
	Abstinence	166 (23.4)	27 (9.1)	193 (19.5)
Treatment history	Treatment experienced	609 (87.8)	277 (93.6)	886 (89.5)
	Treatment naïve	85 (12.2)	19 (6.4)	104 (10.5)
Functional status	Working	668 (96.3)	283 (95.6)	951 (96.1)
	Ambulatory	20 (2.9)	5 (1.7)	25 (2.5)
	Bed ridden	6 (0.9)	8 (2.7)	14 (1.4)
Median age – year		40 (33-48)	34.5 (28-40)	38 (30-45)
Median weight – Kg		56 (49-63)	53 (45-59)	55 (48-62)
WHO stage	1	662 (95.4)	281 (94.9)	943 (95.3)
	2	15 (2.2)	7 (2.4)	22 (2.2)
	3	16 (2.3)	8 (2.7)	24 (2.4)
	4	1 (0.1)	0 (0)	1 (0.1)
HIV viral	≥1000 copies/Ml	174 (25.1)	96 (32.4)	270 (27.3)

load	50-1000 copies/Ml	520 (74.9)	200 (67.6)	720 (72.7)
CD4+ T-cell count	<200 cells/mm^3	254 (36.6)	121 (40.9)	375 (37.9)
	200 to 349 cells/mm^3	250 (36.0)	97 (32.8)	347 (35.1)
	350 to 499 cells/mm^3	111 (16.0)	34 (11.5)	145 (14.6)
	≥500 cells/mm^3	79 (11.4)	44 (14.9)	123 (12.4)
Adherence for treatment	Poor	18 (2.6)	5 (1.7)	23 (2.3)
	Fair	103 (14.8)	82 (27.7)	185 (18.7)
	Good	573 (82.6)	209 (70.6)	782 (79.0)
Presence of ADE	Yes	289 (41.6)	147 (49.7)	436 (44.0)
	No	405 (58.4)	149 (50.3)	554 (56)
Presence of CoMI	Yes	43 (6.2)	30 (10.1)	73 (7.4)
	No	651 (93.8)	266 (89.7)	917 (92.6)
Median hemoglobin level - g/dL		10 (8-12)	9 (8-12)	9 (8-12)
Median serum creatinine - mg/L		0.7 (0.5-0.8)	0.7 (0.5-0.8)	0.7 (0.5-0.8)
Median ALT - IU/L		20 (13-27)	19 (12-26)	20 (13-27)

Key: ADE-adverse drug event, ALT-alanine aminotransferase, CoMI-comorbid illness, CSH-comprehensive specialized hospital, HIV-Human immune deficiency virus, IU-international unit, OI-opportunistic infection, World Health Organization (WHO) stage 1 indicates asymptomatic infection, stage 2 mildly symptomatic infection, stage 3 moderately symptomatic infection, and stage 4 severely symptomatic infection or acquired immunodeficiency syndrome–defining illness.

Efficacy and survival rate

Since the ratio of event in the hazard was smaller, survival mean over median was used to estimate survival time. The mean survival time using Kaplan-Meier analysis was 10.86 months (95% CI: 10.72-10.99). A significant (p=0.003) viral load reduction was obtained through both regimen groups with a higher reduction in the DTG group for a total of 636 out of 694 participants (91.6%) compared to the EFV-based regimen, 253 out of 296 participants (85.5%).

On the basis of Kaplan-Meier analysis in Figure 3, the average time to achieve VL < 200 copies/mL and <50 copies/mL was 10.43 months (95% CI: 10.26-10.60) and 10.65 months (95% CI: 10.48-10.81) in the DTG group while it was 11.23 months (95% CI: 11.11-11.49) and 11.35 months (95% CI: 11.160-11.53) in the EFV group respectively.

There were significant differences in viral load reduction of < 50 copies/mL between the two treatment groups: a total of 479 of 694 participants (69%) in the DTG group and 196 of 296 participants (66%) in the EFV group showed a viral load reduction of < 50 copies/mL. The difference between the two regimen groups was 3 percentage points (CHR=1.28, 95%CI: 1.08-1.51; p=0.004).

A median change from baseline in the viral load at a study period was higher in the EFV treatment group which is 465 cells/mm^3 [interquartile range (IQR), 176 to 1533] than in the DTG-based regimen with 364 cells/mm^3 [IQR, 174 to 879].

Among those patients with a baseline viral load of ≥1000 copies/mL, a total of 66 from 174 participants (38.0 %) in the DTG group and 35 out of 96 participants (36.5%) in the EFV group had undetectable viral load with a difference of 1.5 percentage points (AHR=0.45, 95%CI: 0.37-0.56; p<0.001) Table 2.

A significantly higher number of patients reached a final viral load threshold of < 200 copies/mL in DTG group (601 out of 694 participants [87%]) compared to EFV group (237 out of 296 participants [80 %]) with a risk difference of 7 percentage points (AHR=1.33, 95%CI: 1.15-1.55; p<0.001) Figure 3.

A difference in number of women those show viral load suppression < 50 copies/mL between the DTG group (236 of 324 [73%]) compared with the EFV group (143 from 217 [66%]) was not statistically significant (p=0.422).

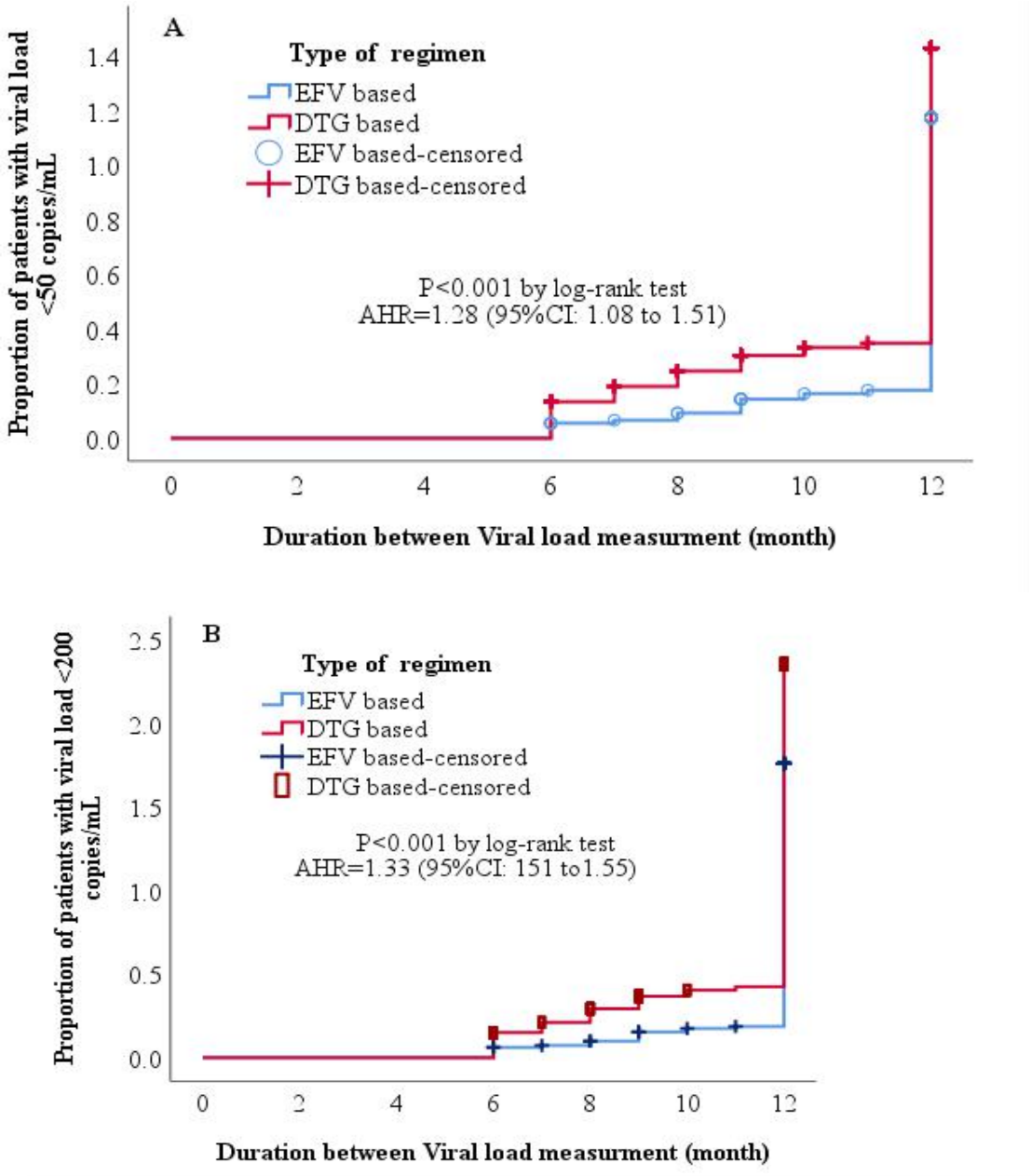

Figure 3: Proportion of patients with viral load <50copies/mL and <200copies/mL at final measurement. Kaplan-Meier plots of time from baseline to the final HIV viral load measurement value of (A) <50 copies/mL and (B) <200 copies/mL at FHCSH, DRH and DSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990).

Among those patients with the higher baseline viral load (≥1000 copies/mL), 37% of them reached a viral load of < 50 copies/mL in the two regimen groups Table 2. Higher

proportion of patients had virologic failure (a viral load of >1000 copies/mL) in the EFV group than in DTG-based regimen (8 out of 296 [2.70%] vs. 11 per 694 [1.59%]).

The median change from baseline in the CD4 T-cell count at one year was higher in the DTG group than in the EFV group (increase of 139 cells/mm^3 [IQR, 69 to 202] vs. 100 cells /mm^3 [IQR, -35 to 164]. This change in CD4+ T-cell count between the two treatment groups was significant (p<0.001); having a higher mean score for DTG (*M*=117) than EFV (*M*=67) with the mean difference of 50 (95%CI: 29-71).

There were a significant differences (p<0.041) in a number of participants had a final CD4+ T-cell count of ≥200 cells/mm^3 in the DTG group (646 out of 694 participants [93%]) compared with the EFV group (256 out of 296 [87%])with a difference of six percentage points (AHR=1.162, 95%CI: 1.01-1.34).

There were a significant differences in mean score (p<0.001) for female participants who had a CD4+ T-cell count increase between DTG group (*M*=124) and EFV group (*M*=60). The magnitude of the differences was higher in DTG group with the mean difference = 64 (95% CI: 3.86-90.54).

Table 2: Kaplan-Meier analysis of good survival outcome ◊ and factors associated for DTG compared to EFV-based regimen among HIV patients in DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 01, 2019 to August 30, 2020 (n = 990).

Variables	Stratum	Mean survival time (month) (95% CI)*		p-value
		DTG	EFV	
Viral load at baseline (copies/mL)	<1,000	10.5 (10.3,10.7)	11.2 (10.9,11.4)	<0.001
	≥1,000	11.1 (10.8,11.4)	11.7 (11.5,11.9)	
CD4+ T-cell count at baseline (cells/mL)	≥200	10.6 (10.4,10.8)	11.2 (10.9,11.5)	0.001
	<200	10.8 (10.5,11.1)	11.6 (11.4,11.8)	
Sex	Female	10.6 (10.4,10.9)	11.3 (11.1,11.6)	0.269
	Male	10.7 (10.4,10.9)	11.4 (11.1,11.8)	
	<15	9.5 (7.8,11.2)	11.5 (11.0,12.0)	

Age (years)	15-24	10.0 (9.3,10.7)	10.3 (9.3,11.3)	<0.001
	25-34	10.3 (9.9,10.7)	11.2 (10.8,11.6)	
	35-44	10.8 (10.5,11.1)	11.5 (11.2,11.8)	
	≥45	10.8 (10.6,11.1)	11.7 (11.4,12.0)	
Type of regimen at baseline	DTG based	7.8 (7.2,8.4)	6.6 (5.8,7.4)	<0.001
	EFV based	11.0 (10.9,11.2)	11.5 (11.3,11.7)	
Prophylaxis given for common OI	Yes	10.2 (10.0,10.5)	11.4 (11.1,11.7)	<0.001
	No	11.1 (10.9,11.3)	11.3 (11.1,11.6)	
Treatment history	Naive	6.9 (6.5,7.4)	6.0 (6.0,6.0)	<0.001
	Experienced	11.1 (11.0,11.3)	11.6 (11.5,11.8)	
Body mass index	18.5-24.5	10.6 (10.5,10.8)	11.4 (11.2,11.5)	0.749
	>24.5	10.5 (8.8,12.2)	12.0 (12.0,12.0)	
	<18.5	10.9 (10.3,11.4)	11.2 (10.5,11.9)	
Bed ridden condition	Yes	12.0 (12.0,12.0)	12.0 (12.0,12.0)	0.004
	No	10.6 (10.5,10.8)	11.3 (11.1,11.5)	
Presence of ADE	Yes	10.8 (10.5,11.0)	11.2 (10.9,11.5)	0.003
	No	10.5 (10.3,10.8)	11.5 (11.2,11.7)	
Presence of opportunistic infection	Yes	11.4 (11.0,11.8)	11.4 (10.8,12.1)	0.003
	No	10.6 (10.4,10.8)	11.3 (11.1,11.5)	
Presence of comorbid illness	Yes	10.6 (9.9,11.3)	11.8 (11.5,12.0)	0.759
	No	10.7 (10.5,10.8)	11.3 (11.1,11.5)	
Adherence for treatment**	Good	10.8 (10.6,11.0)	11.5 (11.3,11.7)	<0.001
	Poor	9.7 (8.2,11.1)	7.2 (5.1,9.3)	

Key: ADE-adverse drug event, Body Mass Index; the weight in kilograms divided by the square of the height in meters, CD4-cluster differentiation, CI-confidence interval, DTG-Dolutegravir, ◊ good survival outcome-viral load reduction to<50copies/mL, EFV–Efavirenz; OI-opportunistic infection; Prophylaxis - co-trimoxazole or isoniazid based prophylaxis, **-185 had fair adherence.*Mean survival time and 95% CI was estimated using Kaplan-Meier curve by each variable individually.

Safety and tolerability

The safety profile of DTG-based regimen was favorable, as compared to the EFV-based regimen. The number of HIV patients who had WHO stage 3 or higher events was 10 out of 694 participants (1.44%) in the DTG group and 7 out of 296 participants (2.36%) in the EFV group (p=0.14) .

A non-significant average weight gain was observed in the DTG group more than the EFV group (0.39 kg vs. 0.32 kg) with a mean difference of 0.07kg (p=0.647). Similarly, the mean weight change was non-significantly higher (p=0.819) in female patients of both regimen groups; 0.48 in DTG and 0.30 in EFV-based regimen (95%CI: -0.004-0.145). Dolutegravir induced weight gain was observed more in participants who had a low body mass index (BMI <18.5kg/m^2) at baseline of the study (AHR=1.33, 95%CI: 1.01-1.75; p=0.043) while high body mass index at baseline (BMI >24.5kg/m^2) was protective for the weight gain (AHR= 0.82, 95%CI: 0.34-1.97; p=0.651).

Even it is not significant (p=0.376), the proportion of experienced any ADE were more in EFV group than DTG group (147 of 296 [49.70%] vs. 289 of 694 [41.64%]. Diarrhea (9.0%), insomnia (6.1%) and nausea (5.5%) were the most common ADE in DTG group while diarrhea (12.5%), nausea (8.8) and insomnia (7.8%) were in EFV group Table 3.

The adherence for treatment by DTG group was better than EFV-based regimens; 573 of 694 (83%) participants in DTG-based regimen vs. 209 out of 296 (71%) participants in EFV-based regimen had good adherence (P<0.001).

HIV patients who took EFV-based regimen non-significantly (p=0.109) experienced disease complications during treatment compared to patients treated with DTG-based regimen (11% vs. 6%). Cardiovascular (9%), cancer (8%), and neurologic (8%) complications were common in EFV whereas cancer (11%), cardiovascular (7%), metabolic (6%) complications were in DTG-based regimen.

The mean increased in serum creatinine was significantly higher in EFV group (0.34) compared to DTG group (0.30) with a mean difference of 0.04 (95%CI: -0.03-0.10; p=0.036) while the mean increased in ALT was 4.25 and 3.86 respectively for DTG and

EFV-based regimens with 0.389 mean difference (95% CI: -1.12-1.90; p=0.613). The average decreased in hemoglobin level of EFV group was non-significantly (p=0.355) larger compared to DTG group; 0.31 vs. 0.29 with mean difference = 0.02 (95% CI: -0.05-0.08).

Table 3: The frequencies of adverse drug events experienced by HIV patients treated with DTG or EFV-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 1, 2019 to August 30, 2020 (n = 990).

Adverse drug event	Regimen		Total
	DTG based	EFV based	
No ADE	405 (58.4%)	149 (50.3%)	554 (56.0%)
Diarrhea	63 (9.1%)	37 (12.5%)	100 (10.1%)
Nausea	38 (5.5%)	26 (8.8%)	64 (6.5%)
Headache	24 (3.5%)	12 (4.1%)	36 (3.6%)
URTI	15 (2.2%)	5 (1.7%)	20 (2.0%)
Insomnia	42 (6.1%)	23 (7.8%)	65 (6.6%)
Vomiting	15 (2.2%)	9 (3.0%)	24 (2.4%)
Nasopharingitis	18 (2.6%)	4 (1.4%)	22 (2.2%)
Cough	9 (1.3%)	5 (1.7%)	14 (1.4%)
Depression	9 (1.3%)	6 (2.0%)	15 (1.5%)
Pyrexia	9 (1.3%)	5 (1.7%)	14 (1.4%)
Fatigue	13 (1.9%)	3 (1.0%)	16 (1.6%)
Dizziness	12 (1.7%)	3 (1.0%)	15 (1.5%)
UTI	16 (2.3%)	6 (2.0%)	22 (2.2%)
Anxiety	4 (0.6%)	3 (1.0%)	7 (0.7%)
Lipodystrophy	2 (0.3%)	0	2 (0.2%)
Total	289 (41.6%)	147 (49.7%)	990 (100%)

Key: ADE-Adverse drug event, DTG-Dolutegravir, EFV-Efavirenz, URTI-Upper respiratory tract infection, UTI-Urinary tract infection

Predictors of survival rate

A bivariate analysis using cox regression model was used to assess the predictors associated with poor survival outcome. These variables at $P < 0.2$ significant level in the bivariate cox regression model were age 25-34 years, sex, presence of OI, bedridden functional status, occurrence of ADE, prophylaxis for common OI, poor adherence for treatment, residence and initial laboratory values of viral load ≥1000 copies/mL and CD4+ T-cell count<200 cells/mm^3. Job type, presence of comorbid illness, type of

regimen and BMI were not statistical significant predictors in bivariate cox analysis to fit multivariate test. All those variables that were predictors for poor survival outcome at 0.2 significant levels in the bivariate cox regression analysis were included in the final multivariate cox regression analysis Table 4. According to the multivariate cox regression model, HIV patients of age group 25-34 years had 32% less risk for poor survival rate compared to patients of age≥45 years old (AHR=0.68, 95%CI: 0.48-0.96 p=0.027). Those patients with bed ridden functional status were almost two times at increased risk of poor survival outcome compared to working groups (AHR=1.98, 95%CI: 1.05-3.73 p=0.035). In addition, patients experienced ADE showed about 37% greater risk of poor survival outcome than those no experienced ADE (AHR=1.37, 95%CI: 1.10-1.71 p=0.005). Presence of OI had 68% greater risk (AHR= 1.68, 95%CI: 1.21-2.34 p=0.002) and prophylaxis given for common OI had 53% less risk for poor survival rate (AHR= 0.47, 95%CI: 0.37-0.60 p<0.001) compared to patients without OI and no prophylaxis respectively. Patients with baseline CD4+ T-cell count <200 cells/mm^3 was almost 1.5 times (AHR=1.46, 95%CI: 1.17-1.83 p=0.001) and baseline VL ≥1000 copies/mL was nearly three times (AHR=2.97, 95% CI: 2.38-3.72 p<0.001) at increased risk of poor survival compared to those had a base line CD4 of ≥200 cells/mm^3 and VL<1000 copies/mL respectively. Poor treatment adherence also increased the risk of poor response (viral load reduction ≥50 copies/mL) by more than two times (AHR=2.25, 95%CI: 1.23-4.11 p=0.009) compared to patients of good adherence. On the other hand, variables of participant sex and residence were not statistically significant as a predictor for poor survival outcome.

Table 4: Bivariate and multivariate cox-regression analysis of predictors associated with viral load reduction of ≥50 copies/mL among HIV treated patients with DTG compared to EFV-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, from September 01, 2019 to August 30, 2020 (n = 990).

Variables		VLR (Copies/mL)		CHR (95% CI)	AHR (95% CI)	P-value
		≥ 50 n=315	<50 n=675			
Age (years)	<15	20	30	1.00 (0.62-1.62)	1.09 (0.66-1.82)	0.733
	15-24	19	52	0.98 (0.60-1.60)	1.00 (0.61-1.64)	0.989
	25-34	51	180	0.66 (0.47-0.92)	0.68 (0.48-0.96)	0.027
	35-44	125	233	0.95 (0.73-1.24)	0.97 (0.75-1.27)	0.838
	≥45	100	180	1	1	
Sex	Female	162	379	0.83 (0.66-1.03)	0.85 (0.67-1.06)	0.148
	Male	153	296	1	1	
Residence	Rural	50	131	0.91 (0.66-1.25)	0.90 (0.66-1.24)	0.518
	Other SC	97	168	1.19 (0.93-1.53)	1.19 (0.93-1.53)	0.171
	Within SC	168	376	1	1	
Functional status	Bed ridden	10	4	1.89 (1.01-3.55)	1.98 (1.05-3.73)	0.035
	Working	290	661	1	1	

Presence of ADE	Yes	165	271	1.36 (1.09-1.69)	1.37 (1.10-1.71)	0.005
	No	150	404	1	1	
Presence of OI	Yes	40	38	1.68 (1.21-2.34)	1.68 (1.21-2.34)	0.002
	No	275	637	1	1	
Prophylaxis for OI	Yes	88	386	0.47 (0.37-0.61)	0.47 (0.37-0.60)	<0.001
	No	227	289	1	1	
Baseline CD4 (cells/mm^3)	<200	150	225	1.45 (1.16-1.81)	1.46 (1.17-1.83)	0.001
	≥200	165	450	1	1	
Baseline VL (copies/mL)	≥1000	169	101	2.90 (2.32-3.62)	2.97 (2.38-3.72)	<0.001
	<1000	146	574	1	1	
Adherence*	Poor	11	12	2.26 (1.24-4.13)	2.25 (1.23-4.11)	0.009
	Good	277	505	1	1	

Key: ADR-adverse drug reaction, AHR-adjusted hazard ratio, CD4-cluster differentiation,CHR-crude hazard ratio, CI-confidence interval, DTG-Dolutegravir, EFV-Efavirenz, OI – opportunistic infection, SC- sub city, VLR –Viral load reduction,*– fair adherence (n=185).

Predictors of safety

458 (46%) out of the total participants took ≥ two other drugs concomitantly with cART regimen. The introduction of new drug (DTG-based regimen) 595 (92.1%), toxicity/side effect 25 (3.9%) drug stock outs 11 (1.7%), forgetfulness 8(1.2%), too ill 4(0.6%) and felt better 3 (0.5%) were the reasons to switch regimens (p<0.001).

On the bivariate cox regression, covariates such as age group15-24 and 35-44 years old, poor adherence, DTG-based initial regimen, OI, naïve treatment history, bedridden functional status, baseline viral load ≥1000 copies/mL, baseline CD4 count <200 cells/mm^3 and student job type were found significant predictors for the occurrence of ADEs at p-value <0.2 and they were candidates for multivariable cox-regression Table 5. Participant sex, marital status, family planning method, presence of comorbid illness, BMI and prophylaxis for common OI were not found to be predictors of ADEs as a result they were not tailored to multivariate analysis. During multivariable cox-regression, age group 15-24 years was more than two times (AHR=2.21, 95%CL: 1.60-3.05; p<0.001) at increased risk and age group 35-44 years was 31% decreased risk (AHR=0.69, 95%CI: 0.53-0.89; p=0.004) for the occurrence of ADE compared to age≥45 years old. Poorly adherent patients had about 3.5 times greater risk for experiencing ADE than patients of good adherence (AHR=3.49, 95%CI: 2.13-5.70; p<0.001). Patients those took DTG-based regimen at baseline were almost three times at higher risk for ADE compared to patients who took EFV-based baseline regimen (AHR=2.85, 95%CI: 1.98-4.09; p<0.001). Moreover, patients infected with OI had 56% greater risk to develop ADE than non-infected patients (AHR=1.56, 95%CI: 1.17-2.09; p=0.003). Treatment naive HIV patients at base line were at more than 10.5 times increased risk to develop ADE than treatment experienced patients (AHR=10.56, 95%CI: 7.21-15.48; p<0.001). The chance of developing ADE in patients with baseline CD4 count <200 cells /mm^3 was increased by 21% compared to those had ≥200 cells /mm^3 (AHR=1.21, 95%CI: 1.01-1.47; p=0.045). Student job type which increases the risk by more than two times (AHR=2.12, 95%CI: 1.55-2.90; p<0.001) were also identified as an independent predictor of cART related ADEs at p-value < 0.05 significance level. Variables of functional status and baseline viral load were not statistical significant predictors for treatment safety.

At any given time HIV patients with comorbid illness had more than thirteen times risk to develop treatment complication (AHR=13.42, 95%CI: 8.52-21.15; p<0.001) than those had no comorbid condition. A unit change in a total number of drugs taken during treatment increases the chance of experiencing ADE by 22% (AHR=1.22, 95%CI: 1.11-1.34; p<0.001) and complications by 83% (AHR=1.83, 95%CI: 1.60-2.09; p<0.001). For each g/dL increase in blood hemoglobin level there was about 5% increases in survival (AHR= 1.05, 95%CI: 1.01-1.09; p= 0.013).

Table 5: Bivariate and multivariate cox-regression analysis of predictors associated with the occurrence of adverse drug event among HIV treated patients with EFV compared to DTG-based regimen at DSH, DRH and FHCSH, Amhara region, Ethiopia, September 01, 2019 to August 30, 2020 (n = 990).

Variables		Adverse drug event		CHR (95% CI)	AHR (95% CI)	P-value
		Yes (n=436)	No (n=554)			
Age (years)	<15	33	17	1.33 (0.91-1.96)	1.44 (0.96-2.17)	0.081
	15-24	53	18	2.16 (1.57-2.98)	2.21 (1.60-3.05)	<0.001
	25-34	115	116	1.18 (0.92-1.53)	1.22 (0.94-1.58)	0.133
	35-44	110	248	0.67 (0.52-0.87)	0.69 (0.53-0.89)	0.004
	≥45	125	155	1	1	
Functional status	Bed ridden	10	4	1.36 (0.73-2.54)	1.37 (0.73-2.58)	0.325
	Working	408	543	1	1	
Presence of OI	Yes	52	26	1.56 (1.17-2.09)	1.56 (1.17-2.09)	0.003
	No	384	528	1	1	
Type of initial regimen	DTG	34	56	2.82 (1.97-4.03)	2.85 (1.98-4.09)	<0.001

	EFV	402	498	1	1	
Adherence for cART	Poor	17	6	3.60 (2.21-5.89)	3.49 (2.13-5.70)	<0.001
	Good	263	519	1	1	
Treatment history	Naive	42	62	10.45 (7.16-15.25)	10.56 (7.21-15.48)	<0.001
	Experience	394	492	1	1	
Baseline CD4 (cells/mm^3)	<200	188	187	1.21 (1.00-1.46)	1.21 (1.01-1.47)	0.045
	≥200	248	367	1	1	
Baseline VL (copies/mL)	≥1000	139	131	1.18 (0.96-1.44)	1.18 (0.97-1.45)	0.104
	<1000	297	423	1	1	
Job type	Un-employed	15	18	1.21 (0.71-2.08)	1.21 (0.71-2.07)	0.491
	Student	62	24	2.08 (1.52-2.84)	2.12 (1.55-2.90)	<0.001
	Others*	249	338	1.12 (0.89-1.40)	1.12 (0.89-1.40)	0.327
	Employed	110	174	1	1	

Key: AHR-adjusted hazard ratio,cART-Combination antiretroviral therapy, CD4-cluster differentiation, CI-confidence interval, COR-crude hazard ratio DTG-Dolutegravir, EFV-Efavirenz, OI – opportunistic infection, VL-viral load, *– Farmer, merchant etc.

6. Discussion

This study aimed to assess the survival rate and safety profile of DTG-based regimen compare to EFV-based antiretroviral therapy. Among 990 study participants, 315 (32%) and 436 (44%) had poor viral load outcome and low safety profile, respectively. Moreover, this 48 week retrospective study confirms that survival rate and safety results were poorer compared with other similar studies conducted for the same duration (Sharon Walmsley, 2015, Kassem Bourgi 2019, Hans-Ju¨rgen Stellbrink, 2013, Charles Kouanfack, 2019, Allan R Tenorio, 2019, Venter et al., 2020, Van Lunzen et al., 2012). Unlike many reference trials discussed here, demographic and clinical characteristics at baseline were not balanced between the treatment groups. The proportion of patients being female, initial viral load≥1000 copies/mL, baseline CD4+ T-cell count <200 cells/mm^3, bed ridden functional status, treatment duration and young median age was higher in EFV-based compared to DTG-based regimen. This is because DTG-based regimen for pregnant and breast feeding mothers, females of child-bearing age without consistent contraceptive method, children younger than ten years and unstable patients is not recommended according to Ethiopia HIV treatment guideline (FMoH, 2018).

There are many controversies regarding the use of DTG for pregnant women among studies those released after Ethiopia HIV treatment guideline had been published. Some articles cautioned the adverse birth outcomes especially neural tube defect from DTG-based regimen whereas in other studies adverse birth outcomes were similar among pregnant women who initiated both EFV and DTG-based regimen (Kenneth Kintu, 2020, Zash et al., 2018). Dolutegravir based regimen reported to have better survival and fewer overall HIV transmission than EFV-based regimen and recommended for all adults regardless of pregnancy, child bearing potential to bring public health benefits and cost effectiveness (Zash et al., 2018, Dugdale et al., 2019, Andrew N Phillips, 2019).

The survival rate based on the proportion of participants who had reduced viral load < 50 copies/mL in both regimen groups (69% in DTG and 66% in EFV) were lower compared to previous studies (Charles Kouanfack, 2019, Sharon Walmsley, 2015, Hans-Ju¨rgen Stellbrink, 2013, Venter et al., 2020, Van Lunzen et al., 2012). The higher survival rate

achieved by previous studies may be due to higher socioeconomic status of patients, availability of baseline resistance screening, the type of NRTI, more frequent and extended follow up schedule and awareness of patients being followed by data collectors. The survival rate was also lower for a viral load threshold of < 200 copies/mL: 86.6% and 80.07% of the participants in the DTG and EFV groups respectively compared to the Charles Kouanfack et al., Cameroon, 2019 (Charles Kouanfack, 2019). The discrepancy could be due to the naïve participants' treatment history and lower baseline immune status in the reference trial as indicated in other studies (Sharon Walmsley, 2015, Charles Kouanfack, 2019, Kenneth Kintu, 2020). Treatment naïve HIV patients comprise only 104 (10.5%) participants and about 38% had CD4<200 cells/mm^3 where as in the Cameroon study, all patients were treatment naïve and 33% had a baseline $CD4^+$ cell count of <200 cells/mm^3.

The average time taken to achieve VL reduction < 50 copies/mL by DTG were favored compared to EFV-based regimen (10.65 months in DTG and 11.35 months in EFV). This result is similar to the clinical trial of 2015 (28 vs. 84 days) (Sharon Walmsley, 2015) and a randomized study conducted for three years (4 months) (Hans-Ju¨rgen Stellbrink, 2013). However, the time to reach this end point was too long in both regimen groups of this study. This might be probably due to the VL measurement carried out at a maximum of two times in our study while it was more frequent in those trial and randomized studies.

A lower number of HIV patients in both regimen group (1.6% in the DTG group and 2.7% participants in the EFV group) had virological failure. This finding largely deviated from the finding of other studies (International study 2.3, 2.9%, Johannesburg 14, 19% and Italy 6.6, 4.8%) (Allan R Tenorio, 2019, Sharon Walmsley, 2015, Venter et al., 2020, Gianotti et al., 2019). The higher virologic failure in reference studies was resulted from their better study design, study set up, follow-up period, time of ART initiation and treatment history as stated in Germany, 2019 (Brehm et al., 2019). In addition, the proportion of patients those had a viral load of < 1000 copies/mL at baseline comprises 73% but all patients of the references had a baseline viral load of ≥ 1000 copies/mL. However, the treatment failure for DTG group (1.6%) was higher as compared to the Cameroon study (<1%) (Charles Kouanfack, 2019). The reason may be due to their higher patients' baseline $CD4^+$ T-cell count and TDF based NRTI as supported by a study of Italy (Gianotti et al., 2019). The treatment failure for EFV group (2.7%) was also higher as compared with the clinical trial of West Central Europe (2.2%), 2020 (Neesgaard et al., 2020). This may be because of the larger sample size, higher median

baseline CD4, higher level of significance together with different study set up and design in the study of Europe. The reason was also supported by a study of Italy (Gianotti et al., 2019).

Even though it was not statistically significant, VL suppression of < 50 copies/mL in women (73% in DTG and 66% in EFV-based regimens) was less than the reports of other comparative studies (Sharon Walmsley, 2015, Charles Kouanfack, 2019, Venter et al., 2020). The subsidizing factor for the observed differences may be due to their higher proportion of women being treatment experienced as treatment history was a predictor for VL reduction in a study of Germany (Brehm et al., 2019). The lower socioeconomic status in our study participants for accessing HIV treatment and inadequate counseling could be another possible issue to be considered.

The median CD4+ T-cell counts increased from baseline was 138.5 in DTG and 100 cells /mm^3 in EFV group of treatment. This is by far lower than the finding of other studies Cameroon 178, 150; International Study 220, 190; SINGLE study 267,208; SPRING-1 study 338,301 and Spain 325,281) (Charles Kouanfack, 2019, Allan R Tenorio, 2019, Sharon Walmsley, 2015, Van Lunzen et al., 2012, Hans-Ju¨rgen Stellbrink, 2013, Blanco et al., 2018). This may be due to the higher baseline immune status of study patients. Likewise, longer follow-up period, rapid initiation of ART, naïve treatment history, robust methodology and their study set up may play a role for the variation. A higher level of non-adherence associated with treatment and prophylaxis, a higher prevalence of OI and low prophylaxis coverage, the poor nutritional condition, low socio-economic level and low educational background in our study participants could also have their own impact for observed inconsistencies as declared in a study of Southern Ethiopia (Abuto et al., 2021).

In this study, patients with bed ridden functional status were almost two times at increased risk of poor survival outcome compared to working groups. Patients experienced ADE and OI also showed about 37% and 68% greater risk of poor survival outcome respectively. Age group 25-34 years had 32% and patients given prophylaxis for common OI had 53% protective effect for survival compared to patients of ≥45 years old

and without prophylaxis respectively. Patients with baseline CD4+ T-cell count <200 cells/mm^3 were almost 1.5 times and baseline VL ≥1000 copies/mL were nearly three times at increased risk of poor survival compared to those had a base line CD4 of ≥200 cells/mm^3 and VL<1000 copies/mL respectively. Poor treatment adherence also increased the risk of poor response (viral load reduction ≥50 copies/mL) by more than two times compared to patients of good adherence. The findings are in line with other studies (Abuto et al., 2021, Siedner et al., 2020). In addition, lower CD4 and higher VL at baseline which are independent predictors of poor survival rate were comparable to studies elsewhere (Sharon Walmsley, 2015, Kenneth Kintu, 2020, Charles Kouanfack, 2019, Abuto et al., 2021, Gianotti et al., 2019). Nevertheless, this result totally deviates from the study of South Africa (Venter et al., 2020). The discrepancy might be due to their better study design and baseline patient characteristics, nutritional status, the healthcare system and resources allocated, study settings with various healthcare professionals' expertise and hospitals' infrastructure.

The survival rate of HIV patients in the presence of OI in DTG was similar with EFV-based regimen. In contrast to this result the viral load reduction achieved by DTG was lower than EFV-based regimen (75% vs. 84%) in TB co-infected patients of a clinical trial conducted in 7 countries (Allan R Tenorio, 2019). This could be due to drug-drug interaction of DTG with Rifampicin and the different in baseline VL of the two regimen groups as justified in other studies (Charles Kouanfack, 2019, Mehtani et al., 2021). On the other hand, younger age group somewhat increased the risk of poor survival rate compared to older patients. This is supported by a study of South Africa in which older patients achieved a higher viral load reduction compared to young one (Venter et al., 2020). There is also a lower virological reduction by the age groups of <18 years in the cohort of United States compared to those patients ≥18 years old in other studies (Sharon Walmsley, 2015, Van Lunzen et al., 2012, Wiznia A, 2015). In contrary to this, age group stratified by 50 years in a trial of North America, Europe, and Australia viral load reduction by older patients were lower than younger age patients (Sharon Walmsley, 2015). This may be due to their better study design, extended study period, higher comorbid condition and lower immune status.

On the issue of safety, the incidence of any ADEs was lower in both regimen groups of this study (49.7% in EFV and 41.6% in DTG groups) compared to previous studies (SPRING 62, 55% and SINGLE studies 54.7,24.2%) (Hans-Ju¨rgen Stellbrink, 2013, Sharon Walmsley, 2015, Venter et al., 2020). These reason for patients developing low ADE possibly related with inadequate follow up time and frequency. In this study the follow-up schedule was too short period and also the frequency of detecting ADE was encountered for few months after starting the treatment. The present study revealed that being treatment naïve had about ten times risk to have ADE than treatment experienced patients and neuropsychiatric ADEs were the most frequent reasons for regimen change in HIV treatment. This is similar to the finding of Italy (Mondi et al., 2019). The prevalence of diarrhea, nausea, headache, fatigue and insomnia were similarly high in DTG-based regimen compared with a study of United States and Canada, 2017 (Benoît Trottier, 2017). The incidence of psychiatric disorders like insomnia, anxiety and depression was lower compared to North America, Europe, and Australia (Sharon Walmsley, 2015). Such variations could be due to lack of standardized method for identifying, assessing, classifying and recording ADEs in our study participants. In this study, there were no abnormal laboratory values and sever ADEs occur that lead to treatment discontinuation. This result is in contrary to the study conducted at 34 sites in France, Germany, Italy, Russia, Spain, and the USA (Hans-Ju¨rgen Stellbrink, 2013). This may be due to our poor and less restrict follow up besides the difference to institutional laboratory service.

The number of participants who had WHO stage ≥3 events which is 1.44% in the DTG and 2.36% in the EFV group was low in this study compared with the study done in Cameroon (5.2%, 5.9%) (Charles Kouanfack, 2019). Patents in this study at baseline were clinically stable (97.5% of participants were stage I and II) and virally suppressed. This good baseline patient condition may be the reason for attaining non-advanced WHO clinical stage.

Age group 15-24 years increased more than two times and age group 35-44 years decreased by 31% of ADE risk compared to age≥45 years old. Being younger in age,

student job type also increases the risk of cART related ADEs by more than two times. In contrary to this result, younger age was protective in a study of Italy (Mondi et al., 2019). The difference may be due to that they record only sever ADE. In addition, they had higher proportion of treatment naïve patients and TDF based NRTI regimen as justified in a study of Aksum (Gebremeskel et al., 2021).

Poorly adherent patients had about 3.5 time greater risk for experiencing ADE than patients of good adherence. Patients those took DTG-based regimen at baseline were almost three times at higher risk for ADE compared to patients who took EFV-based baseline regimen. Moreover, patients infected with OI had 56% greater risk to develop ADE than non-infected patients but these results were not significant and protective factor for developing ADE in Aksum, Ethiopia (0.72,95%CI: 0.45-1.14) (Gebremeskel et al., 2021). The possible reason for this discrepancy may be due to that the study of Aksum counted only sever forms of ADE and had half the sample size of this study. The chance of developing ADE in patients with baseline CD4 count <200 cells /mm^3 was increased by 21% compared to those had ≥200 cells /mm^3 whereas baseline CD4 was non-significant in a study of Italy (Mondi et al., 2019). This may be due to their longer study time, better study setting and design.

The average body weight gain (0.39 kg in DTG and 0.32 kg in EFV) was non-significant and much lower than studies done elsewhere (Kassem Bourgi 2019, Charles Kouanfack, 2019, Taramasso et al., 2020). Being treatment naïve was reported as significant predictors of weight gain in previous studies (Kassem Bourgi 2019, Taramasso et al., 2020) while more of participants in this study was treatment experienced. In addition, this may be due to the poor lifestyle and nutritional status of these study participants.

Type of baseline regimen was not a predictor of survival rate in the current study, whereas it was a significant predictor in a cohort study of Italy (Gianotti et al., 2019). This might be due to their larger sample size, type of NRTI used, strong study method and better study setting.

Limitations of the study

A study design being retrospective all the required information may not be traced from the patient chart and the sample size was also relatively small for generalizability. Since it was based on secondary data it is difficult to ascertain both the survival and safety outcome of DTG over EFV-based regimen. There might be also a difference on the measurement of each study variable across health professionals, which results in under/overestimate the safety and survival outcomes. A viral load measurement schedules were took longer time (6 to 12 months apart) and less frequent in the study settings that the patient may reach an end point early to determine the difference in survival rate. Predictors like blood glucose level, nutritional status and vital signs were not comprised as they were not fully documented on patient register as a result they were totally left out from the analysis.

7. Conclusion

Dolutegravir based regimen showed an improved safety and tolerability profile as compared with the EFV-based regimen for the treatment of HIV infected patients. Age from 15-24 years, presence of OI, increased total number of drugs, type of initial regimen being DTG, poor treatment adherence, naïve treatment history, low baseline CD4+ T-cell count (<200 cells/mm^3) and being a student were the predictors of poor safety outcomes whereas age 35-44 years old was protective.

Dolutegravir based regimen improved survival rate over EFV-based regimen in the treatment of HIV infected patients. Bed ridden functional status, poor treatment adherence, high baseline viral load, low baseline CD4+ T- cell count, lower baseline hemoglobin level, presence of ADE and presence of OI were the predictors of poor survival outcomes however age 25-34 years old and prophylaxis for common OI improve survival rate.

8. Recommendation

It is better to conduct such a study prospectively with extended time period and repeated measure of important indicators. Policy makers should revise guidelines and researchers need to review efficacy and safety of DTG on pregnant mothers and younger children. Local health bureaus in collaboration with other stakeholders need to continually work to upturn patient adherence on their cART and OI prophylaxis and treatment. Health institutions need to strengthen their data recording and file keeping practices and patient follow up. Moreover, more attention should be given to clinically unstable patients who have low CD4 and high viral load measurement.

References

ABEBE MOGES, N., OLUBUKOLA, A., MICHEAL, O. & BERHANE, Y. 2020. HIV patients retention and attrition in care and their determinants in Ethiopia: a systematic review and meta-analysis. *BMC Infect Dis,* 20**,** 439.

ABUTO, W., ABERA, A., GOBENA, T., DINGETA, T. & MARKOS, M. 2021. Survival and Predictors of Mortality Among HIV Positive Adult Patients on Highly Active Antiretroviral Therapy in Public Hospitals of Kambata Tambaro Zone, Southern Ethiopia: A Retrospective Cohort Study. *HIV AIDS (Auckl),* 13**,** 271-281.

ALEMSEGED ABDISSA, D. Y., JANNIK FONAGE, ET AL. 2014. Drug resistance in HIV patients with virological failure or slow virological response to antiretroviral therapy in Ethiopia. *BMC Infectious Diseases* 14**,** 181.

ALICE K. PAU, R. M. G., H. CLIFFORD LANE 2018. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. *Panel on Antiretroviral Guidelines for Adults and Adolescents.*

ALLAN R TENORIO, B. G., CHRISTINE L TALARICO, ET AL. 2019. plasma Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clinical Infectious Diseases. *Clinical Infectious Diseases*.

AMY ZHENG, N. K., MINGSHU HUANG, ET AL. 2018. The cost-effectiveness and budgetary impact of a dolutegravirbased regimen as first-line treatment of HIV infection in India. *Journal of the International AIDS Society* 21**,** e25085.

ANDREW N PHILLIPS, F. V., DIANE HAVLIR, ET AL. 2019. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. *Lancet HIV* 6**,** e116–27.

ANDREW N PHILLIPS, L. B.-M., FRANCOIS VENTER, ET AL. 2020. Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines. *Lancet HIV* 7**,** e193–200.

ANKUR GUPTA-WRIGHT, K. F., JOEP J VAN OOSTERHOUT ET AL. 2020. Virological failure, HIV-1 drug resistance, and early mortality in adults admitted to hospital in Malawi. *Lancet*

ANNE DERACHE, C. C. I., SIVA DANAVIAH, ET AL. 2019. Predicted antiviral activity of tenofovir versus abacavir in combination with a cytosine analogue and the integrase inhibitor dolutegravir in HIV-1-infected South African patients initiating or failing first-line ART. *J Antimicrob Chemother* 74**,** 473–479.

ASTUTI, N. & MAGGIOLO, F. 2014. Single-Tablet Regimens in HIV Therapy. *Infect Dis Ther,* 3**,** 1-17.

AVERT.ORG 2019. HIV drug resistance, found from: https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance.

AYALEW, M. B., KUMILACHEW, D., BELAY, A., GETU, S., TEJU, D., ENDALE, D., TSEGAYE, Y. & WALE, Z. 2016. First-line antiretroviral treatment failure and associated factors in HIV patients at the University of Gondar Teaching Hospital, Gondar, Northwest Ethiopia. *HIV AIDS (Auckl),* 8**,** 141-6.

BAGELLA, P., SQUILLACE, N. & RICCI, E. E. A. 2019. Lipid profile improvement in virologically suppressed HIV-1-infected patients switched to dolutegravir/abacavir/lamivudine: data from the SCOLTA project. *Infect Drug Resist,* 12**,** 1385-1391.

BENOÎT TROTTIER, J. E. L., JUSTIN A KOTEFF6 , ET AL. 2017. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. *Antiviral Therapy,* 22**,** 295–305.

BLAKE MAX, S. V. 2014. Dolutegravir: a new HIV integrase inhibitor for the treatment of HIV infection. *Future Medicine Ltd,* 9(11)**,** 967–978.

BLANCO, J. R., ALEJOS, B. & MORENO, S. 2018. Impact of dolutegravir and efavirenz on immune recovery markers: results from a randomized clinical trial. *Clin Microbiol Infect,* 24**,** 900-907.

BREHM, T. T., FRANZ, M., HUFNER, A., HERTLING, S., SCHMIEDEL, S., DEGEN, O., KREUELS, B. & SCHULZE ZUR WIESCH, J. 2019. Safety and efficacy of elvitegravir, dolutegravir, and raltegravir in a real-world cohort of treatment-naive and -experienced patients. *Medicine (Baltimore),* 98**,** e16721.

BRUZZESE, E., LO VECCHIO, A., SMARRAZZO, A. & AL., E. 2018. Dolutegravir-based anti-retroviral therapy is effective and safe in HIV-infected paediatric patients. *Ital J Pediatr,* 44**,** 37.

CATRIONA WAITT, A. A., JOSHUA GINI, LAURA ELSE 2015 DolPHIN-1 : Randomised controlled trial of dolutegravir (DTG)versus efavirenz (EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy. *PLoS ONE,* 10(9)**,** e0138104.

CHARLES KOUANFACK, M. M.-E., PIERRETTE OMGBA BASSEGA, ET AL. 2019. Dolutegravir-Based or Low-Dose Efavirenz–Based Regimen for the Treatment of HIV-1. *New England Journal of Medicine,* 381**,** 816-826.

COMI, L. & MAGGIOLO, F. 2016. Abacavir + dolutegravir + lamivudine for the treatment of HIV. *Expert Opinion on Pharmacotherapy,* 17**,** 2097-2106.

COTTRELL, M. L., HADZIC, T. & KASHUBA, A. D. M. 2013. Clinical Pharmacokinetic, Pharmacodynamic and Drug-Interaction Profile of the Integrase Inhibitor Dolutegravir. *Clinical Pharmacokinetics,* 52**,** 981-994.

CRUCIANI, M. & MALENA, M. 2015. Combination dolutegravir-abacavir-lamivudine in the management of HIV/AIDS: clinical utility and patient considerations. *Patient Prefer Adherence,* 9**,** 299-310.

CRUCIANI, M. & PARISI, S. G. 2019. Dolutegravir based antiretroviral therapy compared to other combined antiretroviral regimens for the treatment of HIV-infected naive patients: A systematic review and meta-analysis. *PLoS One,* 14**,** e0222229.

CURTIS L, S. C., LIM J , AYLOTT A 2014. Dolutegravir: Clinical and Laboratory Safety in Integrase Inhibitor–Naive Patients. *Clinical and Laboratory Safety in Integrase Inhibitor–Naive Patients, HIV Clinical Trials, 15:5, 199-208, DOI: 10.1310/hct1505-199*.

DEHORITY, W., ABADI, J., WIZNIA, A. & VIANI, R. M. 2015. Use of Integrase Inhibitors in HIV-Infected Children and Adolescents. *Drugs,* 75**,** 1483-97.

DERSEH, B. T., SHEWAYERGA, B., DAGNEW MEKURIA, A. & ADMASU BASHA, E. 2020. Virological Treatment Failure Among Adult HIV/AIDS Patients from Selected Hospitals of North Shoa Zone, Amhara Region, Ethiopia. *Infect Drug Resist,* 13**,** 4417-4425.

DOW, D. E. & BARTLETT, J. A. 2014. Dolutegravir, the Second-Generation of Integrase Strand Transfer Inhibitors (INSTIs) for the Treatment of HIV. *Infect Dis Ther,* 3**,** 83-102.

DUGDALE, C. M., CIARANELLO, A. L., BEKKER, L. G. & AL., E. 2019. Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential: A Modeling Study. *Ann Intern Med,* 170**,** 614-625.

EMILIE R. ELLIOT, X. W., SUVEER SINGH, ET AL. 2018. Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition. *Oxford University Press for the Infectious Diseases Society of America.*

ENDALAMAW, A., MEKONNEN, M., GEREMEW, D., YEHUALASHET, F. A., TESERA, H. & HABTEWOLD, T. D. 2020. HIV/AIDS treatment failure and associated factors in Ethiopia: meta-analysis. *BMC Public Health,* 20**,** 82.

FANTAUZZI, A. & MEZZAROMA, I. 2014. Dolutegravir: clinical efficacy and role in HIV therapy. *Therapeutic Advances in Chronic Disease,* 5**,** 164-177.

FANTAUZZI, A., TURRIZIANI, O. & MEZZAROMA, I. 2013. Potential benefit of dolutegravir once daily: efficacy and safety. *HIV AIDS (Auckl),* 5**,** 29-40.

FMOH 2019. Implementation manual for DTG rollout and ART optimization in Ethiopia. *Federal Ministry of Health, Ethiopia*

FMOH, E. 2018. National consolidated guidelines for comprehensive HIV prevention, care and treatment. *FMoH*.

FOURATI, S., CHARPENTIER, C. & AMIEL, E. A. 2015. Cross-resistance to elvitegravir and dolutegravir in 502 patients failing on raltegravir: a French national study of raltegravir-experienced HIV-1-infected patients. *Journal of Antimicrobial Chemotherapy,* 70**,** 1507-1512.

GATELL, J. M., ASSOUMOU, L., MOYLE, G., WATERS, L. & AL., E. 2017. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. *AIDS,* 31**,** 2503-2514.

GEBREMESKEL, T. G., GEBREYOWHANS, D., ABRHA GESESEW, H. & WARD, P. R. 2021. Incidence and Predictors of Severe Adverse Drug Reaction Among Patients on Antiretroviral Therapy in Tigray, Ethiopia: A Retrospective Cohort Study. *HIV AIDS (Auckl),* 13**,** 641-649.

GIANOTTI, N., LORENZINI, P., COZZI-LEPRI, A., DE LUCA, A., MADEDDU, G., SIGHINOLFI, L., PINNETTI, C., SANTORO, C., MERAVIGLIA, P., MUSSINI, C., ANTINORI, A., D'ARMINIO MONFORTE, A. & GROUP, I. F. S. 2019. Durability of different initial regimens in HIV-infected patients starting antiretroviral therapy with CD4+ counts <200 cells/mm3 and HIV-RNA >5 log10 copies/mL. *J Antimicrob Chemother,* 74**,** 2732-2741.

HANS-JU¨RGEN STELLBRINK, J. R., ADRIANO LAZZARIN ET AL. 2013. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. *AIDS,* 27**,** 1771–1778.

HILL, A. M., MITCHELL, N., HUGHES, S. & AL., E. 2018. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals. *Current Opinion in HIV and AIDS,* 13**,** 102-111.

HILL, J. S. A. A. 2018. Is pricing of dolutegravir equitable? A comparative analysis of price and country income level in 52 countries. *Journal of Virus Eradication* 4**,** 230–237.

IYIDOGAN, P. & ANDERSON, K. 2014. Current Perspectives on HIV-1 Antiretroviral Drug Resistance. *Viruses,* 6**,** 4095-4139.

JASON J. SCHAFER, J. M. C., ELIZABETH M. SHERMAN, ET AL. 2018. HIV pharmacotherapy : the pharmacist's role in care and treatment. *American Society of Health-System Pharmacists*.

JEAN JOEL R. BIGNA, C. S. P. A. S. K.-S. 2016. Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count. *bBMC*.

KANDEL, C. E. & WALMSLEY, S. L. 2015. Dolutegravir - a review of the pharmacology, efficacy, and safety in the treatment of HIV. *Drug Des Devel Ther,* 9**,** 3547-55.

KANTERS, S., VITORIA, M. & DOHERTY, E. A. 2016. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *The Lancet HIV,* 3**,** e510-e520.

KASSEM BOURGI , P. F. R., MEGAN TURNER, ET AL. 2019. Greater Weight Gain in Treatment Naïve Persons Starting Dolutegravir-Based Antiretroviral Therapy. *Clinical Infectious Diseases.* .

KEESHIN, S. W. & FEINBERG, J. 2015. Evaluation of dolutegravir safety for the treatment of HIV-1. *Expert Opin Drug Saf,* 14**,** 141-7.

KENNETH KINTU, T. R. M., JESCA NAKIBUKA ET AL. 2020. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. *Lancet HIV,* 7

LU, D., LU, T., WU, H. & CHE, J. 2013. Challenges for HIV/AIDS therapy. *Adv Pharmacoepidemiol Drug Saf,* 2**,** e120.

LUO, X. L., MO, L. D., SU, G. S., HUANG, J. P., WU, J. Y., SU, H. Z., HUANG, W. H., LUO, S. D. & NI, Z. Y. 2019. Incidence and types of HIV-1 drug resistance mutation among patients failing first-line antiretroviral therapy. *J Pharmacol Sci,* 139**,** 275-279.

M DE MULDER, V. Y., AA WIZNIA, ET AL. 2014. HIV-1 drug resistance prevalence, drug susceptibility and variant characterization in the Jacobi Medical Center paediatric cohort, Bronx, NY, USA. *HIV Medicine,* 15**,** 135–143.

MARCO VITORIA, A. H., NATHAN FORD, ET AL. 2018. The transition to dolutegravir and other new antiretrovirals in low- and middleincome countries – what are the issues? *HIV & Global Hepatitis Programme*.

MCLAUGHLIN, M., WALSH, S. & GALVIN, S. 2018a. Dolutegravir-induced hyperglycaemia in a patient living with HIV. *J Antimicrob Chemother,* 73**,** 258-260.

MCLAUGHLIN, M., WALSH, S. & GALVIN, S. 2018b. Dolutegravir-induced hyperglycaemia in a patient living with HIV. *Journal of Antimicrobial Chemotherapy,* 73**,** 258-260.

MEHTANI, N. J., PURYEAR, S., PHAM, P., DOOLEY, K. E. & SHAH, M. 2021. Infectious Diseases Learning Unit: Understanding Advances in the Treatment of Latent Tuberculosis Infection Among People With Human Immunodeficiency Virus. *Open Forum Infect Dis,* 8**,** ofab319.

MENDOZA, Y., CASTILLO MEWA, J., MARTINEZ, A. A., ZALDIVAR, Y., SOSA, N., ARTEAGA, G., ARMIEN, B., BAUTISTA, C. T., GARCIA-MORALES, C., TAPIA-TREJO, D., AVILA-RIOS, S., REYES-TERAN, G., BELLO, G. & PASCALE, J. M. 2016. HIV-1 Antiretroviral Drug Resistance Mutations in Treatment Naive and Experienced Panamanian Subjects: Impact on National Use of EFV-Based Schemes. *PLoS One,* 11**,** e0154317.

MENÉNDEZ-ARIAS, L., NYAKATO, P. & DAVIES, E. A. 2020. Virologic response to efavirenz-based first-line antiretroviral therapy in children with previous exposure to antiretrovirals to prevent mother-to-child transmission. *Plos One,* 15.

MERCADEL, C. J., SKELLEY, J. W. & KYLE, E. A. 2014. Dolutegravir. *Journal of Pharmacy Technology,* 30**,** 216-226.

MICHAEL R. KEEGAN, A. W., CHRIS HIGGS, ET AL. 2018. Tryptophan metabolismand its relationship with central nervous system toxicity in people living with HIV switching from efavirenz to dolutegravir. *Journal of NeuroVirology* 25**,** 85–90.

MILLER, M., LIEDTKE, M. D., RATHBUN, R. C. & AL., E. 2015. The role of dolutegravir in the management of HIV infections. *Infection and Drug Resistance*.

MISGENA, D. K. 2011. The pattern of immunologic and virologic responses to Highly Active Antiretroviral Treatment (HAART): Does success bring further challenges? *Ethiop J Health Dev*

MONDI, A., COZZI-LEPRI, A., TAVELLI, A., RUSCONI, S., VICHI, F., CECCHERINI-SILBERSTEIN, F., CALCAGNO, A., DE LUCA, A., MAGGIOLO, F., MARCHETTI, G., ANTINORI, A., D'ARMINIO MONFORTE, A. & ICONA FOUNDATION STUDY, G. 2019. Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. *J Int AIDS Soc,* 22**,** e25227.

MONDI, A. C.-L., A. CINGOLANI, A. ET AL 2019. Comparative Neuropsychiatric Toxicity Profile of Dolutegravir versus Efavirenz versus Other Antiretroviral Third Drugs Used either in First-Line or Switch Antiretroviral Therapies (Art): Data from Icona Foundation Study Cohort. *National Institute for Infectious Diseases*.

MZIRAY, S. R., KUMBURU, H. H., ASSEY, H. B., SONDA, T. B., MAHANDE, M. J., MSUYA, S. E. & KIWELU, I. E. 2020. Patterns of acquired HIV-1 drug resistance mutations and predictors of virological failure in Moshi, Northern Tanzania. *PLoS One,* 15**,** e0232649.

NEESGAARD, B., MOCROFT, A., ZANGERLE, R., WIT, F., LAMPE, F., GUNTHARD, H. F., NECSOI, C., LAW, M., MUSSINI, C., CASTAGNA, A., MONFORTE, A. D., PRADIER, C., CHKHARTISVILLI, N., REYES-URUENA, J., VEHRESCHILD, J. J., WASMUTH, J. C., SONNERBORG, A., STEPHAN,

C., GREENBERG, L., LLIBRE, J. M., VOLNY-ANNE, A., PETERS, L., PELCHEN-MATTHEWS, A., VANNAPPAGARI, V., GALLANT, J., RIEGER, A., YOULE, M., BRAUN, D., DE WIT, S., PETOUMENOS, K., BORGHI, V., SPAGNUOLO, V., TSERTSVADZE, T., LUNDGREN, J., RYOM, L. & GROUP, R. S. 2020. Virologic and immunologic outcomes of treatment with integrase inhibitors in a real-world setting: The RESPOND cohort consortium. *PLoS One,* 15**,** e0243625.

ORGANIZATION, W. H. 2016. Global health sector strategy on HIV 2016–2021 towards ending AIDS. *WHO/HIV/2016.05*.

OSTERHOLZER, D. A. & GOLDMAN, M. 2014. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. *Clin Infect Dis,* 59**,** 265-71.

PATEL, D. A., SNEDECOR, S. J., TANG, W. Y., SUDHARSHAN, L., LIM, J. W. & AL., E. 2014. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. *PLoS One,* 9**,** e105653.

PAUL E. SAX, C. J. C., DANIEL R. KURITZKES 2017. *HIV Essentials, found from: https://www.amazon.com/HIV-Essentials-2017-Paul-Sax/dp/1284124703*Jones & Bartlett Learning.

PAUL E. SAX, C. J. C., DANIEL R. KURITZKES. 2014. HIV Essentials *Jones & Bartlett Learning,* Seventh Edition.

PENG, S., TAFAZZOLI, A., DORMAN, E. & AL., E. 2014. Cost-effectiveness of DTG+ABC/3TC versus EFV/TDF/FTC for first-line treatment of HIV-1 in the United States. *Journal of the International AIDS Society,* 17.

RAFFI, F., POZNIAK, A. L. & WAINBERG, M. A. 2014. Has the time come to abandon efavirenz for first-line antiretroviral therapy? *J Antimicrob Chemother,* 69**,** 1742-7.

RAFFI, F., RACHLIS, A., BRINSON, C. & AL., E. 2015. Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naive HIV-infected individuals in three randomized trials. *Aids,* 29**,** 167-174.

RICKY HSU, J. F., CASSIDY HENEGAR, ET AL. 2018. Psychiatric outcomes observed in patients living with HIV using six common core antiretrovirals in the Observational Pharmaco-Epidemiology Research and Analysis database. *Therapeutic Advances in Drug Safety,* 9(12)**,** 675 –686.

ROMINA QUERCIA, J. R., LOUISE MARTIN-CARPENTER, ET AL. 2015. Comparative Changes of Lipid Levels in Treatment-Naive, HIV-1-Infected Adults Treated with Dolutegravir vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Darunavir-Based Regimens Over 48 Weeks. *Clin Drug Investig,* 35**,** 211–219.

RUTHERFORD, G. W. & HORVATH, H. 2016. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. *PLoS One,* 11**,** e0162775.

RUTSTEIN, S. E., CHEN, J. S., NELSON, J. A. E. & AL., E. 2019. High rates of transmitted NNRTI resistance among persons with acute HIV infection in Malawi: implications for first-line dolutegravir scale-up. *AIDS Res Ther,* 16**,** 5.

RUTTER, M. M. A. L. 2018. Dolutegravir in Southern & Eastern Africa and the Right to Choose. *Global Access Project*

SEYLER, L., LACOR, P. & ALLARD, S. D. 2018. Current challenges in the treatment of HIV. *Pol Arch Intern Med,* 128**,** 609-616.

SHARON WALMSLEY, A. B., JUAN BERENGUER, ET AL. 2015. 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. *Brief Report: Clinical Science,* 70**,** 515–519.

SIEDNER, M. J., MOORHOUSE, M. A., SIMMONS, B., DE OLIVEIRA, T., LESSELLS, R., GIANDHARI, J., KEMP, S. A., CHIMUKANGARA, B., AKPOMIEMIE, G., SERENATA, C. M., VENTER, W. D. F., HILL, A. & GUPTA, R. K. 2020. Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase. *Nature Communications,* 11.

SLUIS-CREMER, N., KRYST, J., KAWALEC, P. & AL., E. 2015. Efavirenz-Based Regimens in Antiretroviral-Naive HIV-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Plos One,* 10.

SNEDECOR, S. J., RADFORD, M., KRATOCHVIL, D. & AL., E. 2019. Comparative efficacy and safety of dolutegravir relative to common core agents in treatment-naive patients infected with HIV-1: a systematic review and network meta-analysis. *BMC Infect Dis,* 19**,** 484.

SONG, I., BORLAND, J., CHEN, S. & AL., E. 2014. Effects of enzyme inducers efavirenz and tipranavir/ritonavir on the pharmacokinetics of the HIV integrase inhibitor dolutegravir. *European Journal of Clinical Pharmacology,* 70**,** 1173-1179.

TAHA, H., DAS, A. & DAS, S. 2015. Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS. *Infect Drug Resist,* 8**,** 339-52.

TARAMASSO, L., BONFANTI, P., RICCI, E., OROFINO, G., SQUILLACE, N., MENZAGHI, B., DE SOCIO, G. V., MADEDDU, G., PELLICANO, G. F., PAGNUCCO, L., CELESIA, B. M., CALZA, L., CONTI, F., MARTINELLI, C. V., VALSECCHI, L., CASCIO, A., BOLLA, C., MAGGI, P., VICHI, F., DENTONE, C., ANGIONI, G., MASTROIANNI, A., FALASCA, K., CENDERELLO, G. & DI BIAGIO, A. 2020. Factors Associated With Weight Gain in People Treated With Dolutegravir. *Open Forum Infect Dis,* 7**,** ofaa195.

TEBAS, P., KUMAR, P., HICKS, C. & AL., E. 2015. Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naive adults over 144 weeks. *Aids,* 29**,** 2459-2464.

TZOU, P. L., RHEE, S. Y., DESCAMPS, D. & AL., E. 2020. Integrase strand transfer inhibitor (INSTI)-resistance mutations for the surveillance of transmitted HIV-1 drug resistance. *J Antimicrob Chemother,* 75**,** 170-182.

UNAIDS 2021. Global HIV statistics, found from: https://www.unaids.org/en/resources/fact-sheet.

UNAIDS/WHO/UNICEF, U. W. A. W. H. C. I. T. 2017. HIV Country Profile-Ethiopia *Global AIDS Monitoring*.

VALENTINA MONTESSORI, N. P., MARIANNE HARRIS, ET AL. 2004. Adverse effects of antiretroviral therapy for HIV infection. *JAMC*.

VAN LUNZEN, J., MAGGIOLO, F., ARRIBAS, J. R. & AL., E. 2012. 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,* 12**,** 111-118.

VENTER, W. D. F., SOKHELA, S., SIMMONS, B. & AL., E. 2020. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *The Lancet HIV,* 7**,** e666-e676.

WAINBERG, T. M. A. M. A. 2014. Is Resistance to Dolutegravir Possible When This Drug Is Used in First-Line Therapy? *viruses,* 6**,** 3377-3385.

WALMSLEY, S. L., ANTELA, A., CLUMECK, N. & AL., E. 2013. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. *New England Journal of Medicine,* 369**,** 1807-1818.

WHO 2020. HIV fact sheet, found from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids.

WIZNIA A, A. C., FENTON T 2015 Dolutegravir in 6--12 Year Old HIV Infected Children: 48--Week Results from IMPAACT P1093. *Pediatr Infect Dis J.*

WORKU, E. D., ASEMAHAGN, M. A. & ENDALIFER, M. L. 2020. Epidemiology of HIV Infection in the Amhara Region of Ethiopia, 2015 to 2018 Surveillance Data Analysis. *HIV AIDS (Auckl),* 12**,** 307-314.

YING ZHOU, J. L., JINGEWANG, ET AL. 2016. Prevalence of HIV Antiretroviral Drug Resistance and Its Impacts on HIV-1 Virological Failures in Jiangsu, China: A Cross-Sectional Study. *BioMed Research International*.

YOUNG, F., CRITCHLEY, J. A., JOHNSTONE, L. K. & UNWIN, N. C. 2009. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. *Global Health,* 5**,** 9.

ZASH, R., JACOBSON, D. L., DISEKO, M. & AL., E. 2018. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *The Lancet Global Health,* 6**,** e804-e810.

Annexes

Annex I: Treatment staff information sheet

Name of principal investigator: MeleseAlemnew

Name of Study area: Debretabor, FelegeHiwot, and Dessie hospitals HIV treatment centers

Research budget covered by: Addis Ababa University

Research objective: To assess the safety and survival rate of Dolutegravir compared to Efavirenz based regimen among HIV treated patients in HIV treatment centers at multicenter.

Significance of the study: It is important to reduce the problems of treatment failure, and improve patient's survival, clinical outcome and quality of life as well as to preserve long term efficacy of available drugs. A better understanding of patient safety and HIV resistance to the front line available ART drugs help stakeholders to design better management strategies. In addition to this the study will provide means and information for others to conduct further study on HIV.

Study method: Institution-based, retrospective cohort study will be carried out. To perform this study the required information will be collected from patient chart using structured abstraction tool after we got ethical approval and clearance from the ethics review committee of the school of pharmacy, college of health sciences; Addis Ababa University.

Risks: There will be no threat expected from conducting this study for anyone else.

Beneficial: The study is beneficial to improve the quality of clinical and pharmaceutical care through future interventions based on the findings of this study.

Bonus: Even if the study sites does not gain any direct incentives, the correct and appropriateness of information collected will have a great role in improving the services they delivered in those hospitals.

Confidentialities: The study will not include patient's name and/or address and data will be accessed only by ethically conducted, well trained and experienced health care professionals and analyzed by the principal investigator.

Agreement: Study site representatives and treatment staffs will be expected to be fully

voluntary to give the required and appropriateness data to the study.

Whom to contact: If you have any kind of difficulties about the study, fell-free to contact the principal investigator or advisor:

Principal investigator: MeleseAlemnew, +251-962-811-556, e-mail: melesealemnew2@gmail.com

Advisor: AlemsegedBeyene (Assistant professor), e-mail 'alembeyene98@gmail.com'

Annex II: Data collectors

Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmacology and Clinical Pharmacy, Data collection tool to assess the safety and survival rate of Dolutegravir compared to Efavirenz based regimen in HIV treated patients.

Dear data collector,

First of all I would like to thank you for your willingness to accept my request and to participate as a data collector in this study. This study is believed to be useful for the community in improving health care services provided for HIV. You are selected after observing your interest, skill to communicate and solve problems. A high quality data to change and/or pass influential decision on HIV treatment will be on your hand. You have to be clear on each terms of the data abstraction tool before you are going to collect the data. You are highly responsible to honestly generate the reliable and accurate data and also to keep the information of each chart confidentially. The data will be collected from September 1, 2020 to September 30, 2020 and the reports should be submitted daily.

Annex III: Data abstraction formats; (put √ sign in your answer box)

Part 1: Socio-Demographic Characteristics			
1.1. Unique code number _____			
1.2.Sex Male ☐ Female ☐		1.3. Age in Y or M (for < 5y) ____ ___	
1.4. If female	Pregnant ☐	Non pregnant ☐	Breast feeding ☐
1.5. Weight (in kg)	Before current regimen ____	Current ____ e	
1.6. Nutritional status	BMI (Current)____	MUAC ____	
1.7. Marital status	Single ☐	Married ☐	Divorced ☐ Widowed ☐

1.8. Educational level	No formal education ☐ Primary school ☐ Secondary school ☐ Higher education ☐		
1.9. Family planning method	Not used any ☐ Condom ☐ OCP ☐ Injectable/Implantable ☐ Diaphragm/cervical cap ☐ Intrauterine device ☐ Vasectomy/tubal ligation ☐ Abstinence ☐		
1.10. Residence (current)	Within hospital sub city ☐ Rural area ☐	Other than hospital city ☐	
1.11. Job type	Employed ☐ Unemployed ☐ Student ☐ Other, Specify _____		
1.12. Disclosure status	Disclosed ☐ Not Disclosed ☐		
Part 2: Clinical characteristics			
2.1. Treatment History	Treatment nave ☐ Treatment experienced ☐		
2.2. Duration of ART treatment (in years) _____	2.3. Duration of treatment with current regimen _____		
2.4. WHO staging (Stage I-IV)	Base line _____ At the end of the study period _____		
2.5. Functional status	Working ☐	Ambulatory ☐	Bed ridden ☐
2.6. Developmental milestone	Appropriate ☐	Delay ☐	Regression ☐
2.7. Adverse drug event(Mark all that apply)	No Side Effect ☐ Nausea ☐ Diarrhea ☐ Fatigue ☐ Head ache ☐ Numbness/Tingling/Pain ☐ Rash ☐ Anemia ☐ Abdominal pain ☐ Jaundice ☐ Fat changes ☐ Dizzy, Anxiety, Night Mare, Depression ☐ Others specify _		
2.8. Total # of drugs taken during treatment ☐			
2.9. Opportunistic infections ((Mark all that apply)	PTB ☐ Bacterial pneumonia ☐ Oral candidiasis ☐ Esophageal candidiasis ☐ Oral thrush ☐ Chronic/acute diarrhea ☐ PCP ☐ CNS Toxoplasmosis ☐ Cryptococcal meningitis ☐ Non-Hodgkin's lymphoma ☐ Hepatitis B ☐ Hepatitis C ☐ Bacterial infection ☐ Kaposi sarcoma ☐ Cervical cancer ☐ Others Specify _____		
2.10. Comorbid condition (Mark all that apply)	Diabetic Mellitus ☐ Heart Failure ☐ Hypertension ☐ End stage renal disease ☐ Depression ☐ Malnutrition ☐ Arthritis ☐ Organ transplant ☐ Others Specify_____		
2.11.Complication	If yes; List here _____		

Part 3: Medications	
3.1. Current ART regimen	TDF-3TC-EFV ☐ TDF+3TC+ DTG ☐ AZT-3TC-EFV ☐ AZT+3TC+ DTG ☐ ABC+3TC+EFV ☐ ABC+3TC+ DTG ☐
3.2. Prophylaxis for common Opportunistic infections	CPT ☐ IPT ☐
3.3. Current ART adherence	Good >95% ☐ Fair (85-94%) ☐ Poor (<85%) ☐
3.4. Co-trimoxazole preventive therapy adherence status	Good >95% ☐ Fair (85-94%) ☐ Poor <85% ☐
3.5. If fair or poor adherence for ART what is the reason (Mark all that apply)	Toxicity/side effects ☐ Share with others ☐ Forget ☐ Felt better ☐ Too ill ☐ Stigma, disclosure ☐ Drug stock out ☐ Lost/ran out of pills ☐ Delivery/travel problems ☐ Inability to pay ☐ Alcohol ☐ / Depression ☐ Others, specify …….
3.6. Medications taken for comorbid illness (Mark all that apply)	Antibiotics ☐ Anti-TB ☐ Antihypertensive ☐ Anti-seizure ☐ Anti-hepatitis ☐ Anti-diabetics ☐ Cholesterol lowering agent ☐ Anti-cancer ☐ Anti-asthmatics ☐ anti-pains ☐ Others, Specify _____

Part 4: Data abstraction formats of pertinent laboratory findings (*SI unit*)

At baseline

Scr	ALT	Hgb	CD4 T-cell	Viral load

At the end of the study

Scr	ALT	Hgb	CD4 T-cell	Viral load