Comparison of Outcomes of Tenofovir and Zidovudine Based First-Line Antiretroviral Therapy Regimens at Zewditu Memorial Hospital: Retrospective Cohort Study

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This is to certify that the thesis prepared by Abel Terrefe, entitled "*Comparison of Outcomes of Tenofovir and Zidovudine Based First-Line Antiretroviral Therapy Regimens at Zewditu Memorial Hospital: Retrospective Cohort Study*" and submitted in partial fulfillment for the requirements of the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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Abstract

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Addis Ababa University, 2018

Human immunodeficiency virus (HIV) is one of the major health problems in the world. Nearly 37 million people are living with the disease. Antiretroviral therapy (ART) significantly reduces mortality and morbidity of HIV patients. Despite the successes of ART, high incidence of frequent change of initial therapy has been consistently observed. Tenofovir (TDF) is a first-line antiretroviral (ARV) agent recently introduced in resource limited areas. It is well tolerated and effective in studies from developed countries. However there is limited information on the effectiveness and tolerability outcomes of TDF based regimens in Ethiopia. The aim of this study was to compare the outcomes of TDF and zidovudine (AZT) based regimens focusing on toxicity driven regimen substitution, mortality and lost to follow up. Retrospective cohort study was conducted at Zewditu Memorial Hospital (ZMH). A total of 223 ART naïve patients who started ART between August 31, 2010 and August 31, 2013 were included. Data was collected by review of patients' medication record. Data was analyzed using statistical package for social sciences (SPSS) 20.0. Kaplan-Meier was used to compare survival experience in TDF and AZT groups and Cox regression was used to identify independent predictors of toxicity driven regimen substitution and mortality. The mean standard deviation (SD) age of participants was 37.07 (10.17) years for TDF and 35.27 (7.52) years for AZT groups. Majority of female patients (57.9%) were in TDF group. The risk of toxicity driven regimen substitution was 5 times higher in AZT than TDF group (adjusted hazard ratio (AHR=5.07, 95% CI (1.4-18.33), P=0.013). There was no statistically significant difference in mortality and program failure between TDF and AZT groups. According to this study TDF has superior safety and similar effectiveness as compared to AZT for the treatment of HIV. The finding of this study supports the recent implementation of TDF as a first-line ARV in resourced limited settings.

Key words: ART, TDF, AZT, Toxicity driven regimen substitution, Mortality, Zewditu Memorial Hospital

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List of Abbreviations

ABC	Abacavir
AHR	Adjusted hazard ratio
ADR	Adverse drug reaction
AIDS	Acquired immunodeficiency syndrome
AZT	Zidovudine
ART	Antiretroviral therapy
ARV	Antiretroviral
CHR	Crude hazard ratio
d4T	Stavudine
EFV	Efavirenz
GFR	Glomerular filtration rate
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HBV	Hepatitis B virus
HAART	Highly Active Antiretroviral therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
IQR	Inter quartile range
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OIs	Opportunistic Infections

NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
RCT	Randomized clinical trials
SD	Standard deviation
SPSS	Statistical package for social sciences
3TC	Lamivudine
TDF	Tenofovir
TB	Tuberculosis
UNAIDS	United Nations Program on HIV/AIDS
WHO	World Health Organization
ZMH	Zewditu Memorial Hospital

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1. Introduction

1.1. Background

HIV is one of the major global public health problems. Nearly 37 million people are living with HIV and 1.8 million people are newly infected with HIV every year. In the world's most affected region, Eastern and Southern Africa, the number of new HIV infections and related deaths has shown a decreasing trend since 2010 (UNAIDS, 2017).

The first evidence of HIV infection in Ethiopia was recognized in the early 1980's. The first two AIDS cases were reported in 1986 (FHAPCO, 2007). According to the recent HIV related estimates and projection for Ethiopia, the national adult HIV prevalence is 1.1% (MOH, 2017).

Due to introduction of a triple combination therapy in the mid- 1990s, known as Highly active antiretroviral therapy (HAART), that dramatic, sustained reductions of HIV related mortality and morbidity were observed in HIV patients, resulting a complete change in treatment outcomes (Hogg et al., 1999). Access to ART has shown an enormous progress particularly in developing world. Global coverage of ART reached 46% at the end of 2015. Gains were greatest in the world's most affected region, eastern and southern Africa. ART coverage increased from 24% in 2010 to 54% in 2015, reaching a regional total of 10.3 million. Since 2010 ART averts 7.8 million acquired immunodeficiency syndrome (AIDS) related deaths worldwide (UNAIDS, 2016). In order to further advance therapy, new agents that have minimal impact on co-morbidities and maximize long-term tolerability in the context of earlier diagnosis, earlier initiation and longer duration of treatment are needed (Ray et al., 2016).

In 2010, World Health Organization (WHO) recommended the need for countries to phase out Stavudine (d4T) based regimens because of the drug's long term irreversible side effects. In its place, WHO suggested using AZT or TDF based first-line regimens (WHO, 2010). In 2013, WHO has strengthened the previous recommendations by including TDF/Lamuvidine (3TC)/Efavirenz (EFV) as preferred first-line ART regimen (WHO, 2013).

ART regimens need to be non-toxic and simple to take. Therefore modifying therapy is to be avoided whenever possible. Substitution of ART is defined as any alteration of one or more components of a patient regimen. ART may need to be modified but substitution should be

reasonable. Reasons for changing include treatment failure, toxicity, availability of newer and improved regimen, and emergence of concurrent illnesses such as TB (Takuva et al., 2012; Mekonnen and Molla, 2014; Anlay et al., 2016; WHO, 2013).

Toxicities are the leading cause of substituting initial ART. Many studies have shown the frequent need for partial or total change of initial regimens due to toxicity. Studies in developing countries reported high proportions of toxicity driven regimen substitution: include 70% in Ethiopia (Anlay et al., 2016), 40% in Caribbean, Central and South America (Wolff et al., 2016) and 18% in Uganda, Kenya and Zambia (Macharia et al., 2014).

TDF is well tolerated. The main advantage over AZT is that it does not cause anemia (Arasteh et al., 2009). The regimen TDF/3TC/EFV has additional advantages over other alternative ARV regimens. Its once daily dosing can support adherence, the regimen is not contraindicated for patients on TB treatment unlike those containing the non-nucleoside reverse transcriptase inhibitor (NNRTI) NVP and the pricing is competitive with AZT containing regimens that include EFV (WHO consolidate guideline, 2013).

TDF has shown superior virological and immunological responses as compared to AZT according to clinical trials from developed countries. A randomized control trial (RCT) conducted in six European countries and United State reported AZT/(3TC to have inferior virologic potency compared to TDF/emtrcitabine (FTC). In addition, patients on TDF/FTC showed significantly greater increases in CD4 count as compared to AZT/3TC (190 vs. 158 cells per cubic millimeter (cells/mm^3) (Gallant et al., 2006). A prospective clinical trial that assessed the impact of switching HIV infected patients from AZT/3TC to TDF/FTC obtained that patients switched to TDF/FTC maintained virologic suppression and immunologic control with better tolerability (Arasteh et al., 2009). Similarly, RCT conducted to evaluate impact of switching stable patients on AZT/3TC to TDF/FTC concluded that switching AZT/3TC to TDF/FTC results in improvements in hemoglobin and key lipid parameters and preserve and restores limb fat relative to AZT/3TC (Fisher et al., 2009). In other RCT patients in TDF group showed superior virologic outcome and greater increase in CD4 count (312 cells/mm^3) than AZT group (270 cells/mm^3). And also, more patients in AZT group (11%) discontinued ART due to ADRs than in TDF group (5%) (Arribas et al., 2008).

1.2. Statement of the problem

Antiretroviral therapy (ART) has significantly reduced mortality and morbidity of HIV/AIDS patients. Recently access to ART has increased in low and middle income countries. Clinical guidelines were frequently updated and new recommendations were introduced to improve the existing ART practice. TDF was the second-line option for treatment of HIV in resource limited countries, before its introduction as first-line ARV in 2010 (WHO, 2010). It has shown good safety and efficacy in studies conducted in developed countries (Gallant et al., 2006; Arribas et al., 2008). In one systematic review TDF based regimens have shown superior viral load suppression and tolerated better than AZT based regimens (Dadi et al., 2017). However ART outcomes and toxicities in developed countries differ from that in developing countries due to high prevalence of conditions such as anemia, malnutrition, TB and patients' initial presentation with advanced diseases (Subbaraman et al., 2007).

Despite the fact TDF is effective for treatment of HIV; there are evidences that indicate the need for further investigation on long term outcomes of the drug. There are inconsistent findings on comparative efficacy and safety of TDF compared to AZT based regimens. In some studies TDF was reported to cause greater decline in renal function and to have high risk of proximal tubular dysfunction in naïve HIV patients initiating ART (Horberg et al., 2010). Although in most of early clinical trials no report on discontinuation of TDF due to toxicity (Gallent et al., 2006; Arribas et al., 2008), recently observational study in developed setting has reported significantly high incidence of discontinuation due to TDF associated toxicities (Costarelli et al., 2016). In a retrospective cohort study from Nigeria higher immunological and virologic failure was observed in patients taking TDF/3TC/NVP compared to AZT/3TC/NVP (Scaris et al., 2015). Furthermore, in two systematic reviews the overall mortality among patients who were taking either AZT or TDF based ART regimens was not significantly different (Omeje and Okwundu, 2012; Dadi et al., 2017).

In Ethiopia until 2016, there was no study that compared TDF and AZT based ART regimens. Very recently, few studies were coming out comparing the outcomes of TDF and AZT based regimens. For example, a study in Jimma University has compared the immunological and clinical outcomes of the regimens but it didn't include outcomes related to regimen substitution or toxicities (Ayele et al., 2017a). In addition, a study from Gondar assessed first-line ART

regimen substitution due to any reason including ADRs. From this study, it was observed that ADRs were the major reason for regimen substitution in Ethiopia. According to the study, the risk of changing initial regimen increased nearly 25 times by side effects (Awoke et al., 2016). In Ethiopia there was no study that compared toxicity related regimen substitution in patients taking TDF and AZT based ART regimens.

In general in Ethiopia there is limited data on the comparative outcomes of ART particularly in TDF and AZT based regimens. Hence, this study could be an input to fill the gaps and provides new or supportive evidence to the current recommendations on the use of ART regimens in resource limited areas.

1.3. Literature Review

1.3.1. Antiretroviral Therapy

Antiretroviral therapy (ART) has significantly reduced morbidity and mortality in people living with HIV in resource limited settings (Mills et al., 2011). HAART is a combination of three active ARV agents from two pharmacologic classes, which have shown to inhibit HIV replication, prevent and reverse immune deficiency, and substantially decrease morbidity and mortality. The three primary groups of drugs for treatment of HIV are entry inhibitors, reverse transcriptase inhibitors, and protease inhibitors (PIs). Reverse transcriptase inhibitors consist of two classes. Nucleoside reverse transcriptase inhibitors (NRTIs) are chemical derivatives of purine and pyrimidine base and NNRTIs are those that are not. NRTIs include d4T, AZT, FTC, 3TC, zalcitabine (ddC), abacavir (ABC), didanosine (ddI) and TDF, which is an adenosine-derived nucleotide analog (Tsibris and Hirsch, 2010, Dipiro, et al., 2011). NRTIs are considered the "backbone" of ART and are generally used in combination with a NNRTIs, PIs, or integrase inhibitors. NRTIs are usually given in pairs, such as TDF and 3TC/FTC; AZT and 3TC and ABC and 3TC (Hoffmann et al., 2007; Thompson et al., 2012).

In most studies, majority of participants were on TDF based regimens as reported in studies from developing countries include: in Ethiopia (Tatiparthi and Mamo, 2014), in South Africa (Brennan et al., 2013), in Lesotho (Bygrave et al., 2011), in Zambia (Chi et al., 2010), in Nigeria (Njuguna et al., 2013). In contrast, a study in India reported more patients in AZT group that TDF (Thuppal

et al., 2015). In studies from Ethiopia (Ayele et al., 2017) and Eritrea (Medhanie et al., 2015) equal number of patients were allocated in TDF and AZT groups.

1.3.2. Toxicities of Tenofovir and Zidovudine

Safety concerns and side effects are important when selecting combination ART. ART regimens are associated with different range of toxicities. Most of the NRTIs agents available are generally well tolerated. However, some of the short and long term toxicities associated with this class are treatment limiting. In clinical practice, TDF based regimens have shown lower incidence of ADRs as compared to AZT. For example, in Nigeria, 63.2% and 19.3% ADRs were observed in patients taking AZT and TDF based regimens, respectively (Agu and Oparah, 2013). Similarly in a study from Nigeria, moderate and serious adverse events (leading to drug discontinuations) were significantly higher in patients started ART with AZT than TDF in the first 6 months of treatment (Ouattara et al., 2013). In a retrospective cohort study from India, significant proportion of patients in AZT (47%) than TDF (11%) experienced ADRs. Patients on AZT containing regimens were also 8.7 times (95% CI 4.03-18.88) more likely to experience ADRs compared to patients on TDF containing regimen (Thuppal et al., 2015).

AZT is associated with gastrointestinal intolerance, fatigue, lactic acidosis, anemia and loss of limb fat (Pozniak et al., 2006). Anemia is common in developing countries especially among HIV infected individuals and generally worsens with disease progression. Anemia generally occurs during the first six months of AZT therapy (Hassan et al., 2009; WHO, 2013). In a study of 3312 treatment naive HIV patients in Uganda and Zimbabwe, 6.6% of patients on AZT containing regimens exhibited severe anemia by week 48 (Ssali et al., 2006). In addition, RCT showed that significantly higher risk of severe anemia in patients taking AZT than TDF (14 patients vs 0 respectively) (Gallant et al., 2006). AZT induced anemia is associated with high AZT dosage, increased treatment duration, low CD4 count and preexisting anemia. Lack of neurotoxicity and good central nervous system penetration are some of the advantages of AZT (Hoffmann et al., 2007; Subbaraman et al., 2007).

Tenofovir (TDF) has less adverse effects on blood lipids, fat accumulation, and mitochondrial toxicity than other NRTIs, however gastrointestinal symptoms are common (Birkus et al., 2001; Gallant et al., 2004). Over the past few years, nephro-toxicity has been reported in patients taking TDF. Renal toxicities may manifest as acute Kidney Injury (AKI), chronic kidney disease

(CKD), and features of proximal tubular injury, including fanconi syndrome, isolated hypophosphatemia, and decreased bone mineral density (Fernandez-Fernandez et al., 2011). The incidence of clinically significant renal toxicity in TDF was very low in early RCTs (Gallant et al., 2006; Izzedine et al., 2005; Pozniak et al., 2006).

Nephro-toxicity in TDF is mostly associated with mild to moderate disturbance of renal function. Severe renal toxicity occurs rarely, but a significant proportion of patients developed kidney dysfunction in some studies. In one study graded elevation of serum creatinine in TDF occurred in 2.2 % of patients and the risk is increased through combination with nephro-toxic substances, history of renal insufficiency, sepsis, dehydration, advanced HIV infection and pre-existing hypertension (Nelson et al., 2007). A systematic review on the renal safety of TDF containing ART regimens reported significantly greater loss of kidney function among the TDF recipients, although the study concluded that the clinical magnitude of this effect was modest (Cooper et al, 2010). Furthermore, observational studies in resource poor areas have also reported renal toxicities in patients taking TDF.

A study in Zimbabwe and Uganda, reported 1.3% of severe renal dysfunction in patients taking TDF after 96 weeks but in this study TDF free regimens offered only marginal benefit in improving baseline estimated glomerular filtration rate (GFR) (Reid et al., 2008). In the Pacific Asian cohort, 4.2% of patients developed renal dysfunction during TDF use (Tanuma et al., 2016). Similarly in a retrospective cohort study from Brazil 4% of patients were discontinued TDF due to nephro-toxicity (Neto et al., 2015).

In resource limited settings routine hemoglobin monitoring is mandatory in HIV patients taking ART especially AZT based regimens. If the creatinine test is routinely available, WHO recommended performing baseline estimated GFR before initiating TDF based regimens (WHO consolidated guideline, 2013). Studies compared change in hemoglobin and creatinine clearance to assess the change in renal function and hemoglobin throughout different follow up periods after ART initiation.

The study in Zambia obtained similar mean change in creatinine clearance for TDF (-14.7 and -22.0 ml/min) and AZT (-12.7 and -23.7 ml/min) at 6 and 12 months, respectively (Chi et al., 2010). Similarly in one RCT the median increase in estimated GFR at 96 weeks was reported to

be -1.5 ml/min and -0.3 ml/min in TDF/FTC/EFV and AZT/3TC/EFV, respectively (Pozniak et al., 2006). However, other studies reported a significant reduction in creatinine clearance in patients taking TDF.

In United States a retrospective cohort study reported significantly lower mean change in GFR for TDF groups -4.02, -5.21, -7.42, -11.22 ml/min than non-TDF groups 1.41, 0.53, -1.08, -3.65 ml/min at 12, 24, 52, and 104 weeks respectively (Horberg et al., 2010). In a prospective RCT lower median creatinine clearance values were also obtained among patients receiving TDF (98 vs 106 ml/min) at 24 weeks and (103 vs 106 mL/min) at 96 weeks compared to AZT (Romo et al., 2016).

1.3.3. Toxicity driven regimen substitution

Since treatment options are limited and at least three drugs from two drug classes are typically needed for effectiveness, therapy options need to be maximized by decreasing rates of substituting individual drugs within first-line therapy and reducing switching to more expensive second-line therapy. However, delaying substitutions or switches when there are severe ADRs may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure (WHO, 2016). When ART regimen must be modified or stopped, simple substitution of the offending agent with another ARV in the same class may be done without stopping the entire treatment. In case of severe or life threatening toxicities all ARVs must be stopped (WHO, 2010).

In developed countries, RCTs reported more frequent toxicity driven treatment discontinuation in AZT than TDF based regimens. For example in RCTs toxicity related regimen discontinuations in AZT and TDF groups were 9% and 4% at 48 weeks (Gallant et al., 2006) and11% and 5% at 144 weeks respectively (Arribas et al., 2008). .

The co-formulation of AZT/3TC was a preferred choice when it was first introduced in 1997, but is recently considered an acceptable alternative regimen to TDF/3TC. Several African countries adopted TDF as a first-line ARV medication in accordance with WHO recommendation (Hoffmann et al., 2007; WHO, 2013). Limited researches have examined regimen substitution in relation to the WHO policy change recommending the substitution of d4T with TDF in first-line ART. Majority of observational studies in low and middle income countries have compared

single drug substitutions (defined as changing one NRTI for another within first-line ART) amongst patients on TDF, d4T and AZT based regimens using routine clinical program data. According to most of the study's findings' AZT based regimens were substituted more frequently as compared to TDF based regimens. The proportions of toxicity driven regimen substitution reported in patients on AZT and TDF based regimens respectively includes: 13% and 0.7% in east Africa (Macharia et al., 2014), 36% and 3% in India (Thuppal et al., 2015). Anemia was the most frequent reason for regimen substitution in AZT and renal dysfunction in TDF based regimens (Anlay et al., 2016; Macharia et al., 2014; Rajesh et al., 2014).

Studies conducted in resource limited areas have reported different rates of toxicity driven regimen substitutions. In patients on TDF and AZT based regimens, the rate of toxicity driven regimen substitution was reported to be 3 and 8.1 per 100 PYRs in Lesotho (Bygrave et al., 2011), 9 and 27 per 100 PYRs in Zambia (Chi et al., 2010) and in South Africa 1.3 and 5.1; 14.4 and 6.3; 2.6 and 8.5 per 100 PYRs (Velen et al., 2013; Brennan et al., 2013; Njuguna et al., 2013) respectively.

Most of the studies reported an increased risk of toxicity driven regimen substitution in patients on AZT as compared to TDF based regimens. For example, in Lesotho, patients on AZT based regimens were more than twice as likely to experience toxicity driven regimen substitution as compared to TDF (Bygrave et al., 2011). Two studies in South Africa reported 2.8 and 4.4 fold higher risk of toxicity related drug substitution in AZT than TDF based regimens (Brennan et al., 2013; Velen et al., 2013). In the South African study (Brennan et al., 2013) when substitution restricted to the NRTIs (TDF and AZT), the risk of single drug substitution in AZT was 4.5 fold higher than TDF (Brennan et al., 2013). Studies have also compared the time to the occurrence of toxicity driven regimen substitution. Another study from South Africa also reported a hazard of 0.38 for TDF as compared to AZT (Njuguna et al., 2013). In Zimbabwe, the mean number of days before toxicity driven regimen substitution were 388 and 618 for AZT and TDF based regimens respectively (Mudzviti et al., 2015). In South Africa, the median time to single drug substitutions were 2 months for TDF based regimens and 3.7 months for AZT based regimens (Brennan et al., 2013). In contrast a study in South Africa reported patients on TDF based regimens to have shorter median time to drug change due to ADRs (1.5 years) than AZT (2 years) (Njuguna et al., 2013).

In addition to the ART regimens, other factors also reported to have significant association with toxicity driven regimen substitution by different studies. Age is one of the factors reported to be associated with toxicity driven regimen substitution. The study from South Africa showed that patients aged 40 years or older were more likely to have toxicity driven regimen substitution than patients younger than 40 years of age (Njuguna et al., 2013). On the other hand, a study showed higher risk of toxicity driven regimen substitution in patients aged 18-25 and older than 50 years than patients aged 30-40 years (Brennan et al., 2013). Studies identified female sex as a predictor of toxicity driven regimen substitution (Brennan et al., 2013; Chi et al., 2010; Njuguna et al., 2013). However, in studies from Zambia (Chi et al., 2010) and South Africa (Velen et al., 2013), age and sex had no effect on toxicity driven regimen substitution, respectively. Additionally, patients started on NVP based ART had 1.4 fold higher risk of single drug substitution as compared to EVF based regimens in the South African study (Brennan et al., 2013).

1.3.4. Efficacy of Tenofovir and Zidovudine

1.3.4.1. Mortality and Loss to follow up

Poor retention in HIV care after patients started ART is one of the major challenges of the ART program in Ethiopia (FHAPCO, 2014). Discontinuation of ART particularly loss to follow up can be devastating for patients' lives and also facilitates the occurrence of virologic failure and which in turn could lead to an increased chance of HIV transmission (Giordano et al., 2007). In Africa early mortality is an obstacle to the effectiveness of ART. A retrospective cohort study in Ethiopia reported high rate of mortality in the first three months treatment (Mengesha et al., 2014). In Zambian cohort high mortality rate (13.5 per 100 PYRs) was observed in the first 90 days of treatment initiation and most of the early mortalities were observed in patients started on AZT based regimens (Chi et al., 2010). However the overall mortality rate in TDF and AZT groups was comparable in most of the studies from similar areas.

A retrospective cohort study from Ethiopia reported 3.68% and 4.48% death among patients on TDF and AZT respectively. The study also reported 2.9% and 4.3% of loss to follow up in TDF and AZT groups respectively (Ayele et al., 2017a). In Lesotho mortality rate was 5.1 per 100 PYRs and 7.5 per 100 PYRs in TDF and AZT groups respectively (Bygrave et al., 2011). Similarly in South Africa mortality rate was reported to be 9.2 and 11.1 per 100 PYRs in TDF and AZT groups respectively (Velen et al., 2013).

In resource limited areas, findings on comparative risk of death was inconsistence among patients on TDF and AZT based regimens. Studies from Lesotho (Bygrave et al., 2011), Ethiopia (Ayele et al., 2017) and South Africa (Chi et al., 2010) reported a non-significant difference in overall mortality between AZT and TDF groups. However other studies from similar settings have obtained different findings.

A study in South Africa showed patients on AZT based regimens to have 1.4 times higher risk of mortality compared to patients on TDF based regimens (Velen et al., 2013). On the other hand a study from Nigeria obtained 1.88 times higher risk of death in patients on TDF based compared to AZT based regimens (Eguzo et al., 2014). Similarly a study from Ethiopia reported 1.9 times higher risk of death in patients on TDF than AZT base regimens (Awoke et al., 2016).

Some studies compared the time to death between TDF and AZT groups. In a study from Ethiopia the mean time to death was 713.46 days in TDF and 709.57 days in AZT group without statistical significant difference between the two groups (Ayele et al., 2017a). Time to death in TDF and AZT groups was also similar in a study from South Africa (Njuguna et al., 2013).

Studies have defined loss from care and death as a composite outcome to compare factors associated with these outcomes. Some of the composite outcomes for loss to follow up and death include: programmatic failure in South Africa (Chi et al., 2010), and drop out in Uganda (Asiimwel, et al., 2016). A study from Nigeria defined discontinuation as a composite outcome of death, loss to follow up, transfer out and withdraw from the program (Scaris et al., 2015). In Nigeria attrition was referred to patients who stopped treatment or confirmed dead or loss to follow up (Odafe et al., 2012).

In the study from Uganda patients on TDF based regimens have shown a 1.4 fold higher risk of drop out compared to patients on AZT based regimens (Asiimwel, et al., 2016). Similarly the study from Nigeria obtained 2.6 times higher risk of attrition in TDF based regimens than AZT based regimens during the first 12 months of follow-up and similar risk of attrition was observed after 12 months of follow up (Odafe et al., 2012).

Persistently low CD4 cell count despite ART-mediated viral suppression is associated with increased risk of mortality. For example, HIV-infected individuals with CD4 counts < 200 cells/mm3 despite at least 3 years of suppressive ART showed a 2.6 fold greater risk of mortality

than those with higher CD4 cell counts (Engsig et al., 2014). Most of the studies in resource limited areas have shown CD4 count at baseline as an independent predictor of death.

In the Zambian retrospective cohort study patients with baseline CD4 count < 50cells/mm^3 had nearly 4 times higher risk of death than patients with baseline CD4 count > 200 cells/mm^3 (Chi et al., 2010). A study in Ethiopia reported 18% reduction in the risk of mortality as a unit increase in baseline CD4 count (Ayele et al., 2017a). The other study in Ethiopia Somali region found 2.7 times higher risk of mortality in patient with CD4 count < 50 cells/mm^3 than > 200 cells/mm^3 at baseline (Damtew et al., 2015). In the other study from Ethiopia patients with CD4 count 201-300 cells/mm^3 at baseline were 60% less likely to die than patients with baseline CD4 count ≤ 200 cells/mm^3 (Biadgilign et al., 2012). Moreover a study in Nigeria reported more than 3 times higher mortality in patients with baseline CD4 count < 200 cells/mm^3 compared to those patients with CD4 count >500 cells/mm3 (Eguzo et al., 2014). Baseline WHO clinical stage is another risk factor for mortality by some studies.

A study in Ethiopia Somali region showed patients on WHO stage III/IV to have 7.36 times higher risk of mortality than those patients on WHO stage I/II at baseline (Damtew et al., 2015). In the other study from Ethiopia patients on WHO clinical stages I, II and III at baseline had 84%, 66% and 76% lower odds of mortality respectively compared to patients on WHO clinical stage IV at baseline (Setegn et al., 2015). A study from Zimbabwe reported a 1.4 fold higher risk of attrition in patients who were WHO stage IV at baseline than patients with stage I/II. Similarly in Zambia patients on WHO stage IV had 2.31 times higher risk of death as compared to those patients on WHO stage I/II at baseline (Chi et al., 2010). Other clinical and demographic characteristics are also reported to have association with mortality in different studies.

The study in South Africa reported female patients to have an increased risk of mortality and loss from care than males (Njuguna et al., 2013), whereas other studies obtained an increased risk of death and loss to follow up in males than females (Asiimwel, et al., 2016; Odafe et al., 2012; Mekuria et al., 2015; Apollo et al., 2014). Age is also one of the factors associated with mortality. In Uganda patients aged < 28 years showed 1.4 times higher risk of mortality (Asiimwel, et al., 2016). In contrast in Nigeria patients aged > 45 years had 3.6 times higher risk of mortality than patient aged 25-34 years (Engsig et al., 2014). Two studies reported an increased risk of mortality in patients with low hemoglobin at baseline than those patients with normal

hemoglobin (Chi et al., 2010; Asiimwel et al., 2016). Studies also reported baseline weight as a risk factor for mortality and/or loss from care. For example a study from Zimbabwe reported twice higher risk of mortality and/or loss from care in patients with baseline weight < 45 kilogram than > 60 kilogram (Apollo et al., 2014).

1.3.4.2. Immunological Outcome

Antiretroviral therapy (ART) response is usually based on clinical endpoints (i.e., infections, death, and quality of life) or surrogate markers (i.e., predictors of the clinical endpoints). For years CD4 counts have been used as a surrogate marker in resourced limited areas. More recently HIV RNA serum levels have been employed as surrogate markers in resource limited areas (WHO, 2013). Virological, immunological and clinical outcomes are the basis of evaluating success of ART. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. Clinical success is said to have been achieved when there is a reduction in clinical endpoints such as AIDS defining illnesses or death (DHHS, 2015; WHO, 2013).

Tenofovir (TDF) has shown superior efficacy as compared to AZT in most of the studies from developed countries. Randomized control trial (RCT) assessed the efficacy and safety of treatment switch from AZT/3TC to TDF/FTC concluded that virologic and immunologic controls were maintained after regimen switch (Arasteh et al., 2009). In the other RCT among 517 treatment-naive patients taking TDF/FTC/EFV or AZT/3TC/EFV, viral suppression rates were significantly higher among patients taking TDF/FTC compared with AZT/3TC (84 versus 73 %, respectively) (Arribas et al., 2008). In resource limited areas many studies have compared an increase in baseline CD4 count in patients taking TDF and AZT based regimens. Different studies reported significant difference in CD4 count increment from baseline among TDF and AZT based regimens.

A retrospective cohort study in Ethiopia reported greater improvement in the overall mean CD4 count in TDF group (321.7 cells/mm^3) as compared to AZT group (299.4 cells/mm^3) at the end of two years follow up period (Ayele et al., 2017b). In South Africa, patients on TDF showed greater annual CD4 count increment (83.9 cells/mm^3) than AZT (73.0 cells/mm^3) (Velen et al., 2013). On the other hand, some studies reported that AZT based regimens to have equivalent or greater change CD4 count compared to patients on TDF based regimens.

A study from Nigeria reported higher CD4 count increment in patients on AZT/3TC/NVP (221.1 cells/mm^3) than TDF/3TC/NVP (208 cells/mm^3) (Scarsi et al., 2015). In addition, CD4 count increment in patients on TDF and AZT based regimens showed no significant difference in other studies. A study in India obtained equivalent increment in CD4 count between patients started in TDF (212 cells/mm^3) and AZT (208 cells/mm^3) (Gaikwad et al., 2015). The other study in India (Thuppal et al., 2015) reported an increment in CD4 count of (388 cells/mm^3) and (359 cells/mm3) in TDF and AZT based regimens respectively. Additionally, a study in India tertiary hospital found no significance difference in mean CD4 count change between TDF (322.95 cells/mm^3) and AZT (358 cells/mm^3) (Hemasri et al., 2016). A retrospective cohort study in Eritrea showed similar change in mean CD4 count in TDF (351.2 cells/mm^3) and AZT (392.8cells/mm^3) at 24 months of follow up (Medhanie et al., 2015). Furthermore, in Nigeria similar change in CD4 count was reported in TDF and AZT groups, in which the change in CD4 counts was +123 and +90 (cells/mm^3) in the two groups respectively at 6 month of therapy, (Ouattara et al., 2013).

2. Objectives

2.1. General Objectives

To compare the outcomes of TDF and AZT based regimens among treatment naïve HIV/AIDS patients started first-line ART from August 31, 2010 to August 31, 2013 in ZMH.

2.2. Specific objectives

- ✓ To compare time to toxicity driven regimen substitution between TDF and AZT groups
- ✓ To compare time to death between TDF and AZT groups
- ✓ To compare time to program failure between TDF and AZT groups
- ✓ To compare change in estimated GFR and hemoglobin from baseline in TDF and AZT groups
- ✓ To compare change in CD4 count from baseline in TDF and AZT groups
- ✓ To assess the association of toxicity driven regimen substitution with the regimen groups
- ✓ To assess the association of mortality with the regimen groups

3. Methodology

3.1. Study Design and Setting

This study was based on retrospective cohort study design which generated data through review of patient treatment records. The study was conducted in Zewditu Memorial Hospital (ZMH), which is affiliated with Tikur Anbessa Specialized Hospital of Addis Ababa University. It is found in Kirkose sub city, Woreda 08, Addis Ababa, Ethiopia. More than 100,000 patients visit the hospital annually for different health services. The hospital has 872 clinical and non-clinical staffs. The services given in the hospital include: cardiac, diabetic, internal medicine, surgery, pediatrics, gynecology and obstetrics, psychiatry, neurology, dermatology, dental care, dialysis, pharmacy and ART. The first ART service in Ethiopia started in 2005 at ZMH.

3.2. Population

3.2.1. Source and Study Population

All HIV/AIDS patients attending ART at ZMH ART clinic from August 31, 2010 to August 31, 2013 were the source population. The study population included all HIV/AIDS patients started ART on TDF or AZT based regimens at ZMH ART clinic that fulfilled the inclusion criteria of the study during the study period.

During the study period, ART was initiated for HIV patients with CD4 count < 350 cell/mm3 or for those patients with WHO stage III and IV disease. The first-line ART regimens consisted of NRTI backbone AZT, TDF, d4T or ABC with 3TC and either EFV or NVP. The ART regimen selection was based on clinical and laboratory results and medical contraindications. Tenofovir is prescribed for those patients with adequate creatinine clearance (>50 ml/min). Zidovudine was prescribed for those patients with hemoglobin value greater than 10 g/dl at ART initiation and it is also the preferred regimen in patients with diabetics and hypertension. After initiation of ART patients were appointed on 2 weeks after initiation and then every month.

3.3. Inclusion and Exclusion Criteria

3.3.1. Inclusion Criteria

- HIV/AIDS patients 15 years old and above
- HIV/AIDS patients who started ART on TDF or AZT based regimens during the study period

3.3.2. Exclusion Criteria

- Patients with incomplete demographic and clinical information
- Patients who initiated ART with estimated GFR value ≤ 30 ml/minutes
- Patients who initiated ART with baseline hemoglobin value ≤ 7 mg/dl
- Patients who had prior ART experience
- HIV/AIDS patients on TB treatment and pregnancy that resulted regimen substitution, regimen substitution that didn't involve TDF or AZT or regimen substitution with unknown (not registered) reason.

3.4. Sample Size and Sampling Technique

3.4.1. Sample Size

The sample size was determined by using a two population proportion formula through EPI INFO Stat Calc program with the assumption of 95 % level of confidence, 5 % of marginal error, and taking prevalence of toxicity driven regimen substitution 3% and 8.1% for TDF and AZT based regimens respectively from similar study in Lesotho (Bygrave et. al., 2011). Using the above information the sample size was calculated to be 634. This sample size was assumed to have a 1:1 ratio between the two cohort groups.

By taking three years data from ART registration book at ZMH ART clinic, the total number of patients started ART on AZT and TDF based regimens was 138 and 941 respectively. Due to small number of patients started on AZT based regimens, the sample size was reduced using the following sample size reduction formula to 245.

$$nfinal = \frac{n1}{1 + \frac{nt}{Nr}}$$

Where n1-the calculated sample size in each groups

nt- total calculated sample size

Nr- number of patients in each regimen

nfinal- corrected final sample size

3.4.2. Sampling Technique

Study samples were selected by using systematic random sampling method. Therefore by using sampling interval 2 for AZT (k=2.42) and 6 for TDF (k=5.95), 190 and 67 cases in TDF and AZT groups were reviewed respectively. Due to lack of major baseline information, empty patient folder, and regimen substitution because of other reasons, the final number of patients in this study was 164 and 59 in TDF and AZT groups respectively (Fig. 1).

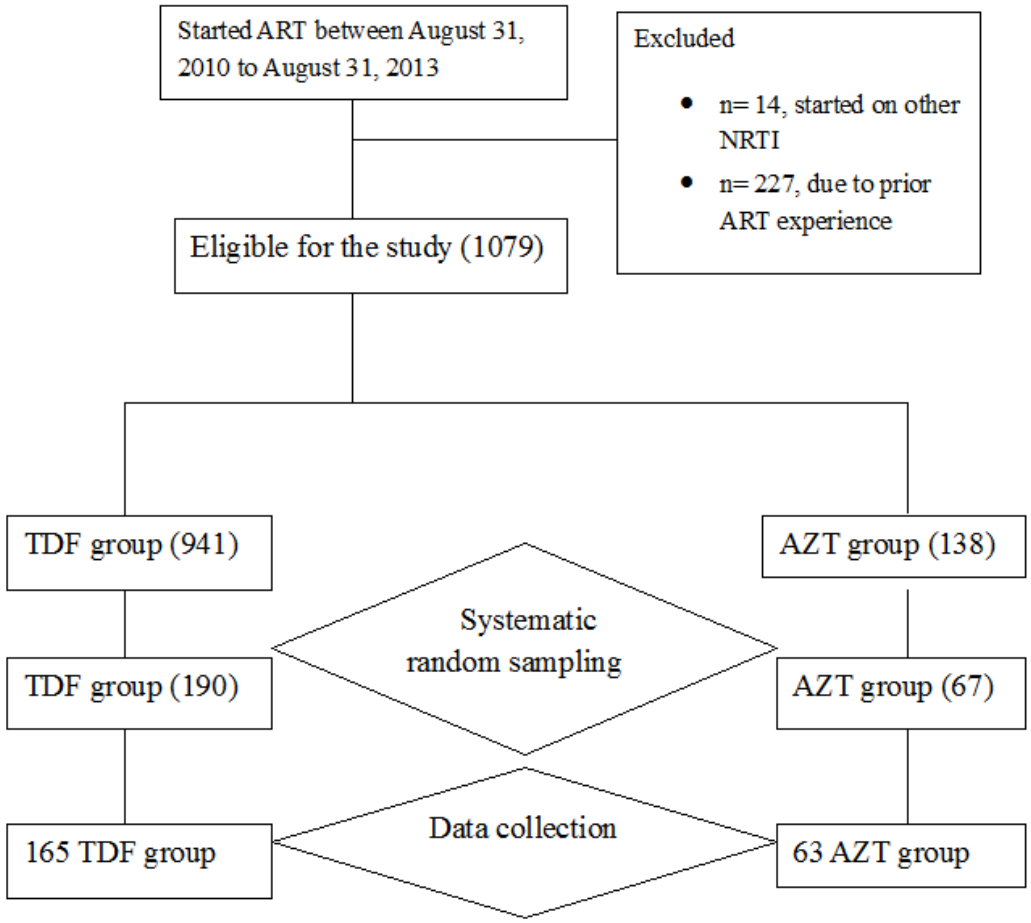

Fig 1: Sample recruitment chart for patients initiated antiretroviral therapy from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

3.5. Study Variables

3.5.1. Independent Variables

Main exposure variables: TDF and AZT groups.

Socio demographic characteristics: Age and Sex.

Baseline clinical characteristics: CD4 count, hemoglobin, estimated GFR, weight, WHO clinical stage, ART regimens (NRTIs and NNRTIs), OIs, TB treatment, concomitant chronic diseases, OI prophylaxis, and pregnancy.

3.5.2. Dependent Variables

3.5.2.1. Primary Outcome Variables

- Time to toxicity driven regimen substitution
- Time to death
- Time to program failure

3.5.2.2. Secondary Outcome Variables

- Change in CD4 count
- Change in hemoglobin
- Change in estimated GFR

3.6. Data Collection Procedures

For the process of data collection two nurses and two pharmacists from ZMH ART clinic were assigned and trained for one day about the method of data collection. Data abstraction format was developed for collecting the relevant patient data (Annex 1). It contained socio demographic, clinical, laboratory and ART follow-up information. Patient medical record and ART patients' information sheet were used to extract socio-demographic and clinical information. Data abstraction form was completed for each eligible patient.

3.7. Data Analysis and Interpretation

Data were entered to computer by using EPI INFO Version 3.5.1. Then it was exported to SPSS 20.0 for analysis. Summary descriptive statistics for continuous baseline characteristics and change in CD4 count, GFR and hemoglobin at 6, 12 and 24 months were tabulated and the variables were assessed for normality. The decision on the assumption of normality was made

based on the aggregate results obtained from Kolmogorov-Smirnov test, skewness and kurtosis statistics, histogram and Q-Q plots. Furthermore, critical values, estimated 95% range, and the difference in mean and median values were computed from the descriptive table and used as an addition evidence for the decision of normality (Barton B. and Peat J.). All continuous baseline variables fulfilled the assumption of normality except estimated GFR. The change in CD4 count, estimated GFR, and hemoglobin at 24 month also fulfilled the normality assumption, however, the changes in CD4 count, estimated GFR, and hemoglobin at 6 and 12 months had skewed distribution.

Creatinine clearance was calculated by Cockcroft-Gault method as follows:

$$\frac{\big((140 - Age) \times (weight\ )\big) \times 0.85\ if\ female}{(Serum\ creatinine \times 72)}$$

To calculate incident rate of the primary outcomes (toxicity driven regimen substitution, mortality and program failure), the total duration of follow up was expressed in PYRs. The total duration of follow up for those patients who developed the outcomes was calculated from the time of ART initiation to the development of the outcomes. The follow up duration for those patients who did not develop the outcomes was calculated from the time of ART initiation until the last visit. The incident rate was calculated as follow and reported in 100PYRs.

$$Incident\ rate =$$
$$number\ of\ patients\ with\ the\ outcomes \div total\ outcome\ free\ duration\ of\ follow\ up$$

The changes in CD4 count, estimated GFR, and hemoglobin at 6, 12, 24 months were calculated by subtracting baseline values from the values at 6, 12 and 24 months.

Continuous variables were described using mean (SD) and categorical variables were described using percentages and frequencies. Patient characteristics at ART initiation by initial NRTI (TDF and AZT) were compared using chi-square test for categorical variables, independent samples t-test for continuous variables with normal distribution and Mann-Whitney U test for continuous variables with skewed distribution. The changes in CD4 count, estimated GFR, and hemoglobin in TDF and AZT groups at 24 month were compared with independent samples t-test but at 6 and

12 months of follow up Mann-Whitney U test was used to compare the changes in the two groups.

Time zero was considered the date of ART initiation and patients were followed for two years. Follow up was censored at the first of: toxicity driven regimen substitution, death, loss to follow up, transfer out or still in care at the database closure. The Kaplan–Meier curve was used to estimate the duration to treatment outcomes. Log rank test was used to compare survival curves between TDF and AZT based regimens. Bi-variate Cox regression model was used to test the effect of covariates on the outcomes. Variables with p-value ≤ 0.25 in bi-variate Cox-regression were considered as candidates for multivariable regression. Hazard ratio with 95% CI was used as measure of strength of association and p-value < 0.05 was considered to declare a statistical significance results.

3.8. Ethical Considerations

Ethical clearance was obtained from Addis Ababa University, School of Pharmacy ethical review board. In addition, permission was obtained from ZMH to access patients' medical records. The reviewed patient information was reported with a code assigned to represent each patient. This was done to protect the exposure of patients' personal information.

3.9. Operational Definitions

Primary Treatment Outcomes: in this study toxicity driven regimen substitution, death, and lost to follow up were considered as the primary treatment outcomes.

Secondary Treatment Outcomes: Changes in CD4 count, GFR, and hemoglobin at 6, 12 and 24 months of follow ups from the values at baseline (ART initiation) were the secondary treatment outcomes.

TDF group: regimen containing TDF as one of the NRTI backbones with either EFV or NVP as NNRTI backbone.

AZT group: regimen containing AZT as one of the NRTI backbones with either EFV or NVP as NNRTI backbone.

Toxicity driven regimen substitution- substitution of ART caused by ADRs and involved either TDF or AZT.

Death- defined as confirmed death from medical records

Loss to follow up: defined as any patient whose last clinic or laboratory record was before closure of the study, in the absence of a recorded treatment stop reason or death.

Program failure: Comprised mortality and loss to follow up outcomes.

4. Results

4.1. Socio-demographic Characteristics

In this study, overall 223 HIV/AIDS patients who started on TDF and AZT based first-line ART from August 31, 2010 to August 31, 2013 were included. Females comprised 53.4% of patients. Majority of TDF (57.9%) and AZT (59.3%) groups were females and males, respectively. The mean age of the study participants was 36.60 years (SD=9.55). Majority of patients in TDF (64.0%) and AZT (71.2%) were aged younger than 40 years old. Most of the study participants 97(43.5%) were married. Regarding to educational status, 113(50.7%) of patients were completed secondary school and 14(6.3%) had no formal education. In comparison of the demographic characteristics of the two groups, there was statistically significant difference in terms of sex only (Table 1).

Table 1: Comparative socio-demographic characteristic of patients started on Tenofovir and Zidovudine based antiretroviral therapy from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

Characteristics		TDF group (n%)	AZT group (n%)
Sex			
	Male	69 (42.1)	35 (59.3)
	Female	95 (57.9)	24 (40.7)
Age (years)			
	<40	105 (64.0)	42 (71.2)
	≥40	59 (36.0)	17 (28.8)
	Mean (SD)	37.07 (10.17)	35.27 (7.52)
Educational status			
No education		12 (7.3)	2 (3.2)
Primary education		40 (24.4)	14 (22.2)
secondary education		81 (49.4)	35 (55.6)
Tertiary education		31 (18.9)	12 (19)
Marital status			
Never married		47 (28.7)	18 (30.5)
Married		70 (42.7)	27 (45.8)
Divorced		30 (18.3)	9 (15.3)
Widowed		17 (10.4)	5 (8.5)

TDF= Tenofovir, AZT= Zidovudine

4.2. Initial Regimens

In this study, 164 (73.5%) patients were on TDF. Majority of the patients 173 (77.6%) used EFV as NNRTI backbone. In TDF and AZT groups, the NNRTI EFV was used in 138 (84.1%) and 35 (59.3%) patients respectively (Fig. 2). The overall mean follow up duration of the cohort was 538.0 (SD=265.54) days. The mean duration of follow ups for TDF and AZT groups were 555.54 (SD=254.93) and 489.24 days (SD=289.78), respectively.

In this cohort patients were followed for different periods of time. Participants in TDF group stayed on follow up for a minimum of 30 days and maximum of 730 days, on the other hand participants in AZT group were stayed a minimum of 60 days and maximum of 730 days. Overall the patients were followed for a total of 32,908.33 PY of observation. Within the follow up period, patients in TDF group were followed for a total of 25,008.33 PYRs and patients in AZT group were followed for a total of 7,900.0 PYRs.

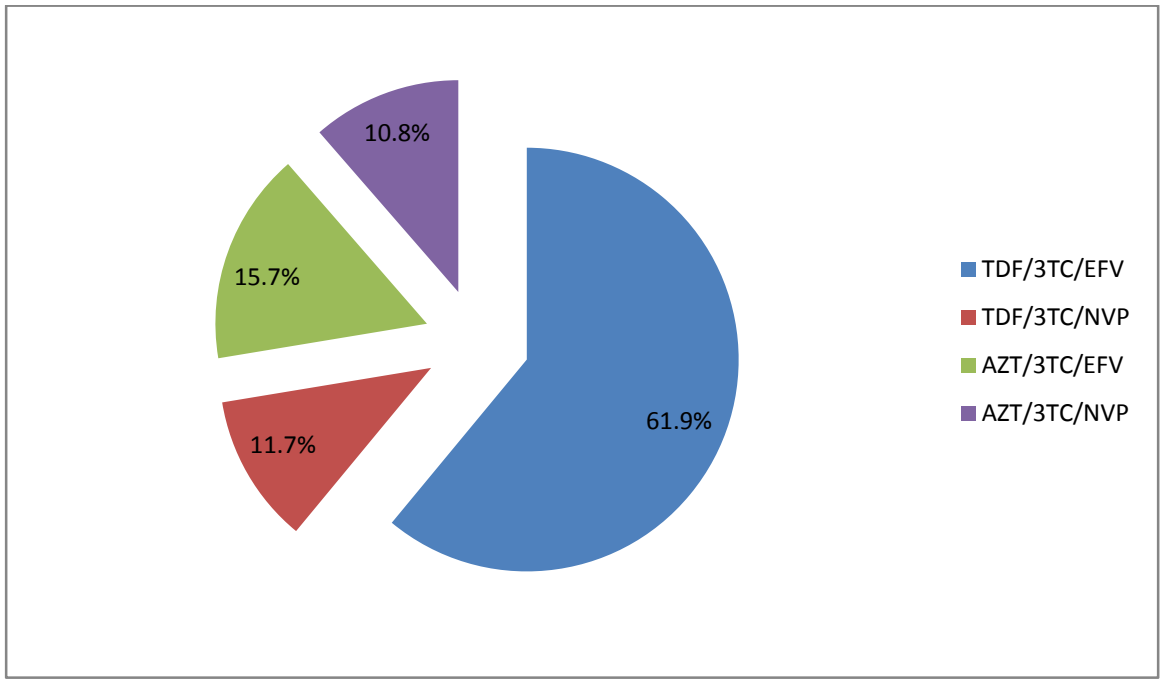

Fig 2: Proportions of Tenofovir and Zidovudine based antiretroviral therapy regimen started from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

4.3. Clinical Characteristics

The overall mean baseline CD4 count of the cohort was 154.46 cells/mm^3 (SD=89.31). More than 50% of patients were started with baseline CD4 count 50-199 cells/mm^3. Within TDF and AZT groups, 56.7% and 47.5% patients respectively started with baseline CD4 count 50-199 cells/mm^3. Equivalent proportions of patients in TDF (15.2%) and AZT (15.3%) group were started with baseline CD4 count < 50 cells/mm^3.

The overall median (IQR) baseline estimated GFR in TDF and AZT group were 111.09 ml/min (37.73) and 99.38 ml/min (30.05) respectively. The mean (SD) hemoglobin values in TDF and AZT groups were 13.45 g/dl (1.83) and 14.6 g/dl (1.8) respectively. Patients in TDF (64.0%) and

AZT (76.3%) initiated with baseline estimated GFR 60-120 ml/min. In AZT group there was no patient with baseline estimated GFR < 60ml/min, whereas, in TDF group 2(1.2%) patients initiated with baseline estimated GFR <60ml/min. Most of patients in AZT group (61.0%) were with baseline hemoglobin > 14 g/dl, while in TDF group majority of patients (62.8%) started with baseline hemoglobin 10-14 g/dl. In addition, in AZT group there was no patient with baseline hemoglobin < 10mg/dl. In contrast, 4(2.4%) patients in TDF group initiated with baseline hemoglobin <10 g/dl.

Almost half 83(50.6%) patients in TDF group were on WHO clinical stage III and IV at baseline, in contrary to majority 36(61.0%) patients in AZT group were on WHO clinical stage I and II. Almost similar proportion of women (7.4%) in TDF and (8.3%) in AZT groups were pregnant during ART initiation. Patients started ART in TDF group (13.4%) were on TB therapy, while less (3.4%) of patients in AZT group were on TB therapy during ART initiation. At ART initiation, (19.5%) and (11.9%) of patients in TDF and AZT groups had OIs respectively. Patients in TDF (85.4%) and AZT (84.7%) were taking OIs prophylaxis at ART initiation. Regarding comparison of clinical characteristics, there was statistically significant difference in baseline estimated GFR, hemoglobin, TB treatment and NNRTIs. Comparative baseline clinical characteristics are described in Table 2.

Table 2 Comparative clinical characteristic of patients started on Tenofovir and Zidovudine based antiretroviral therapy from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

Characteristics		TDF group (n%)	AZT group (n%)	P value
CD4 count at ART initiation (cells/mm3)				0.369
	< 50	25 (15.2)	9 (15.3)	
	50-199	93 (56.7)	28 (47.5)	
	≥ 200	46 (28)	22 (37.3)	
	Mean (SD)	151.23 (89.27)	163.44 (89.57)	
Estimated GFR (ml/min)	< 60	2 (1.2)	0 (0)	0.014
	60-120	105 (64)	45 (76.3)	
	> 120	57 (34.8)	14 (23.7)	
	Median (IQR)	111.09 (37.73)	99.38 (30.05)	
Hemoglobin (g/dl)				< 0.005
	< 10	4 (2.4)	0 (0)	
	10-14	103 (62.8)	23 (39)	
	>14	57 (34.8)	36 (61)	
	Mean (SD)	13.45 (1.83)	14.6 (1.8)	
Body weight (Kilograms)	Mean (SD)	56.73 (11.66)	58.42 (8.86)	0.253
WHO clinical stage				0.125
	I and II	81 (49.4)	36 (61)	
	III and IV	83 (50.6)	23 (39)	
NNRTI				< 0.005
	EVP	138(84.1)	35 (59.3)	
	NVP	26(15.9)	24 (40.7)	
Pregnancy				
	yes	7(7.4)	2 (8.3)	0.874
	No	88(92.6)	22 (91.7)	
TB treatment				0.033
	Yes	22(13.4)	2 (3.4)	

Table 2 (Continued)

Characteristics		TDF group (n%)	AZT group (n%)	P value
OIs				0.137
	Yes	32 (19.5)	7 (11.9)	
	No	132 (80.5)		
OIs prophylaxis				0.48
	Yes	140 (85.5)	50 (84.7)	
	No	24 (14.6)	9 (15.3)	
Concomitant				0.21
chronic disease	Yes	4 (2.4)	4 (6.8)	
	No	160 (97.6)	55 (93.2)	

TDF-Tenofovir, AZT- Zidovudine, ART- Antiretroviral therapy, GFR- Glomerular filtration rate, WHO- World health organization, NNRTIs- Non-nucleotide reverse transcriptase inhibitors, TB- Tuberculosis, OIs- Opportunistic infections, SD- Standard deviation

4.4. Description of ART Treatment Outcomes

The primary outcomes were observed among 71(31.8%) patients in the two years follow-up of this cohort. Among those who were initiated with TDF 48(29.3%) patients experienced the events. Of these toxicity driven regimen substitution, death and loss to follow up accounted for 4(2.4%), 14(8.5%), and 30(18.3%) respectively. While among those who were initiated with AZT 23 (39.0%) patients experienced the events. Of these toxicity driven regimen substitution, death and loss to follow up accounted for 8 (13.6%), 7 (11.9%) and 8 (13.6%) respectively. A total of 101 (61.6%) and 34 (57.6%) patients stayed on their initial regimen after starting with TDF and AZT respectively (Fig 3).

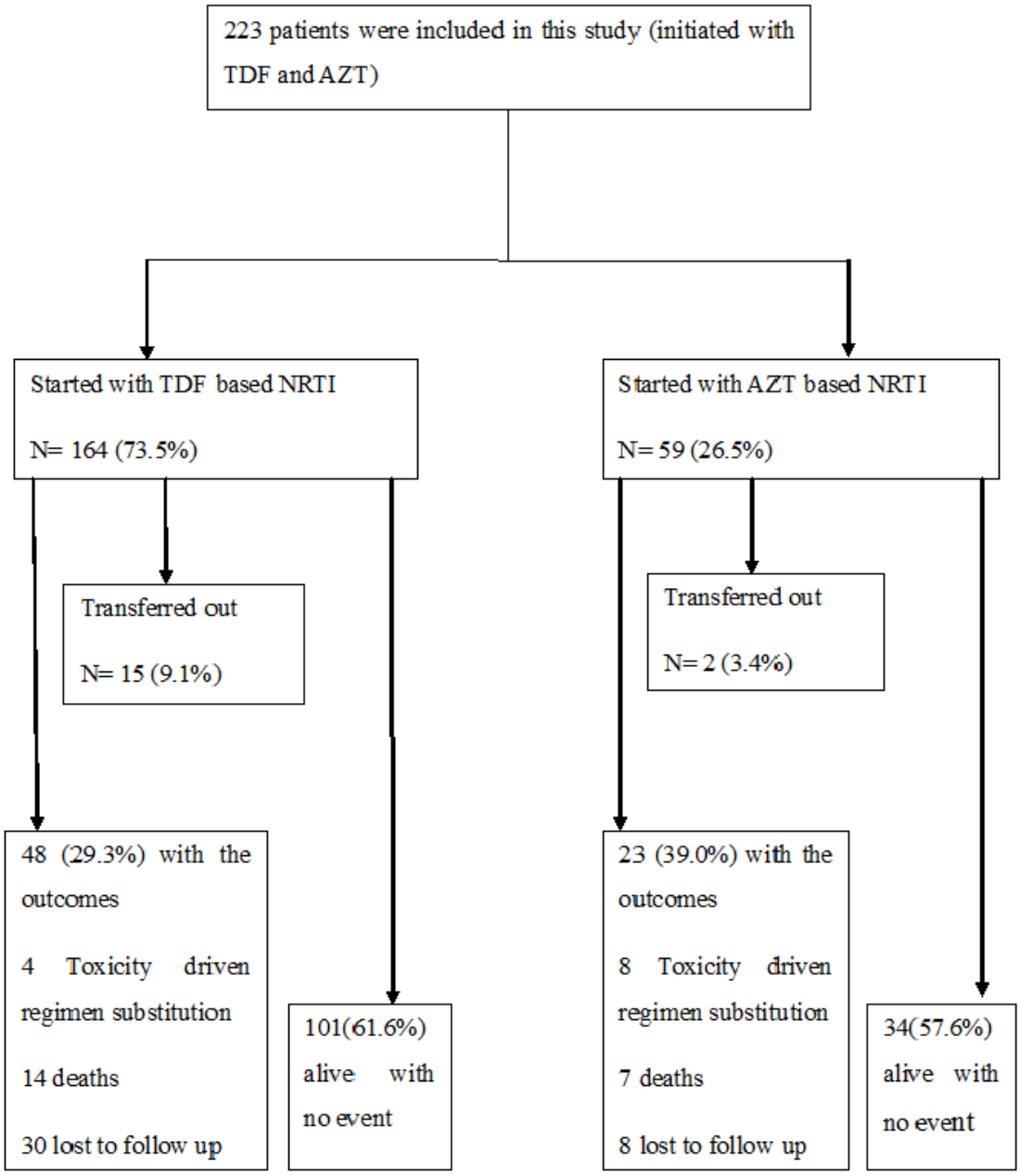

Fig 3: Schematic presentation showing the outcomes in patients started antiretroviral therapy from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

4.5. Safety of Antiretroviral Therapy

4.5.1. Time to Toxicity Driven Regimen Substitution

Over the two years of ART, 12 (5.4%) patients had toxicity related regimen substitution. Of this 4 (2.4%) were from TDF and 8 (13.6%) from AZT group. In TDF group the estimated toxicity driven regimen substitution was 1%, 2%, 3% and 3% at 6, 12, 18 and 24 months respectively. In AZT group the estimated toxicity driven regimen substitution was 6%, 12%, 17%, and 17% at 6, 12, 18, and 24 months respectively (Table 3).

Table 3: Table 3 Estimates of cumulative toxicity driven regimen substitution in patients started on Tenofovir and Zidovudine based antiretroviral therapy from August 31, 2010 to August 31, 2013 at Zewditu Memorial Hospital

Regimen category	Interval start time in month	Number entering Interval	Number of toxicity driven regimen substitutions	Cumulative proportion of survival at the end of interval
TDF	0	164	1	0.99
	6	137	0	0.99
	12	125	2	0.98
	18	114	1	0.97
	24	101	0	0.97
AZT	0	59	3	0.94
	6	47	3	0.88
	12	36	2	0.83
	18	34	0	0.83
	24	34	0	0.83

TDF- Tenofovir, AZT- Zidovudine, n=223

The mean survival time for toxicity driven substitution was 718.26 and 641.83 days in TDF and AZT groups respectively. Patients exposed to TDF had favorable survival experience; and the difference was significant as shown by the Kaplan-Meier survival estimate p=0.001 (fig. 4). The

overall rate of toxicity driven regimen substitution for the cohort was 3.65 per 100 PYR (CI 95%: 1.88-6.37). TDF based regimens substituted at a rate of 1.6 per 100 PYR (CI 95%: 0.43-4.1) compared with 10.13 per 100 PYR (CI 95%: 4.36-19.95) for AZT based regimens.

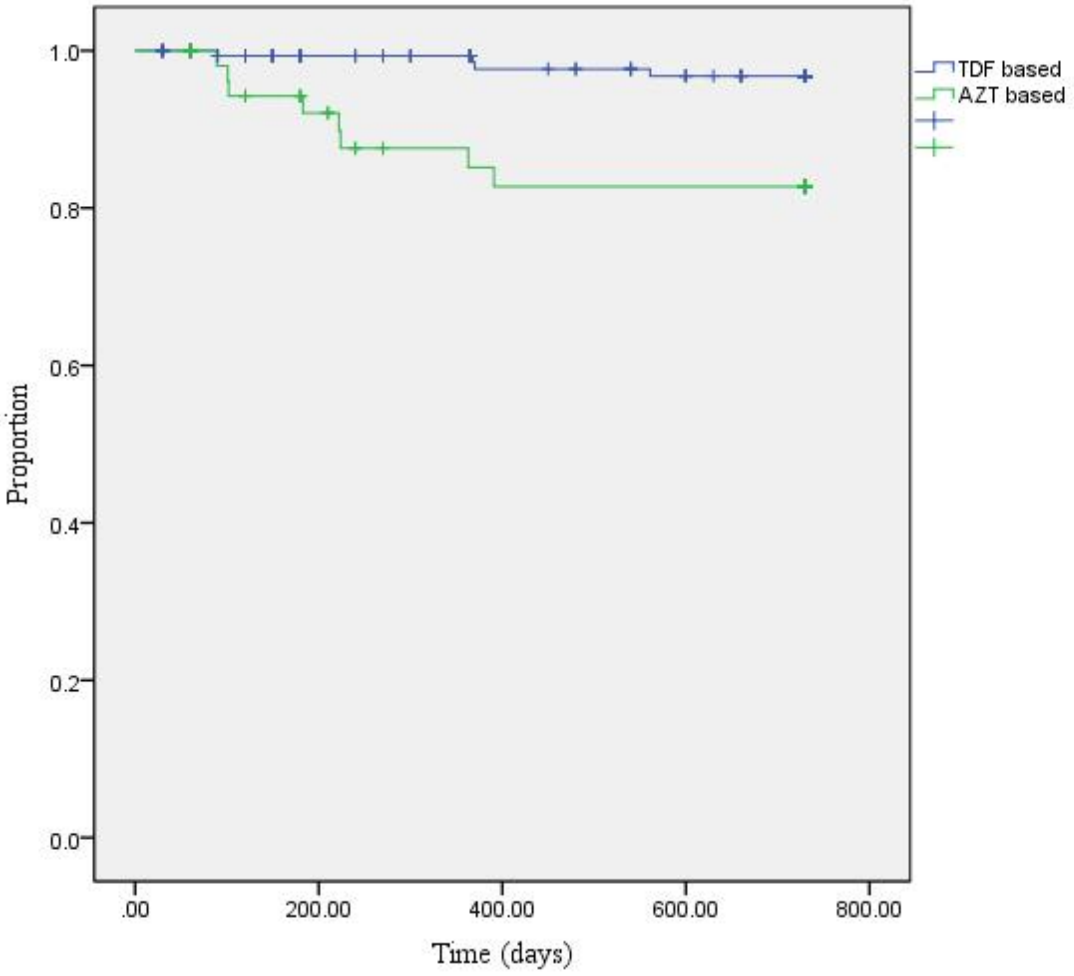

Fig. 4 Survival estimate for toxicity driven substitution in patients initiated on Tenofovir and Zidovudine based regimens at Zewditu Memorial Hospital from August 31, 2010 to August, 31, 2013

4.5.2. Association between Toxicity Driven Regimen Substitution and Treatment Groups

Both bi-variate and multi-variate Cox regression techniques were used to investigate the independent predictors of toxicity driven regimen substitution. In bi-variate Cox-regression, sex, age, NRTI group, baseline body weight, hemoglobin, and concomitant chronic diseases showed

significant association with toxicity driven regimen substitution ($p < 0.25$). Therefore these variables were retained in multi variable Cox regression analysis with the treatment groups.

In multi variable analysis, NRTI groups showed significant association with toxicity driven regimen substitution. Patients in AZT group were 5 times more likely to have toxicity driven regimen substitution compared to patients in TDF group (AHR=5.07, 95% CI (1.4-18.33), P=0.013) when adjusted for sex, age, hemoglobin, weight and concomitant chronic diseases (Table 4).

Table 4: Crude and Adjusted Cox Proportional Hazard Regression for Predictors of Toxicity Driven Regimen Substitution in Patients on Tenofovir and Zidovudine based regimens from August 31, 2010 to August, 31, 2013 Zewditu Memorial Hospital

Variables	CHR (95% CI)	P value	AHR (95% CI)	P value
TDF based	1	0.003	1	0.013
AZT based	6.34 (1.91-21.05)		5.07 (1.4-18.33)	

The analysis adjusted for sex, age, hemoglobin, body weight, concomitant chronic diseases. TDF-Tenofovir, AZT-Zidovudine, ART- Antiretroviral therapy, CHD- Crude hazard rate, AHR- Adjusted hazard rate, GFR- Glomerular filtration rate, WHO- World health organization, NNRTIs- Non-nucleotide reverse transcriptase inhibitors, TB-Tuberculosis, OIs- Opportunistic infections, SD- Standard deviation

4.5.3. Change in Hemoglobin

In TDF group, hemoglobin levels were available in 116 (70.7%), 76 (46.37%), and 25 (15.24%) patients at 6, 12 and 24 months of follow ups respectively. On the other hand, in AZT group 39(66.1%), 25(42.4%) and 17(28.81%) patients had hemoglobin measurements at 6, 12 and 24 months of follow up respectively. The median (IQR) hemoglobin level at 6 and 12 months were 13.8 (1.88) and 13.7 (2) g/dl in TDF and 14.3(2.3) and 14.5 (4.35) g/dl in AZT groups respectively. At the end of follow up (2 years) the mean (SD) hemoglobin levels were 14.15 (1.32) and 13.84 (1.32) g/dl in TDF and AZT groups respectively.

The change in hemoglobin at 6 month of follow up showed a significant reduction from baseline in AZT group, however the change in hemoglobin at 12 and 24 month of follow ups didn't show statistically significant differences among TDF and AZT groups (Table 5).

Table 5: Change in Hemoglobin in Patients Started Antiretroviral Therapy in Tenofovir and Zidovudine based regimens from August 31, 2010 to August, 31, 2013 at Zewditu Memorial Hospital

	TDF group	AZT group	P value
6 month	0.05 (1)**	-0.3 (1)**	0.005
12 month	0.1 (2)**	-0.1 (1)**	0.319
24 month	0.72 (0.32)*	-0.29 (0.47)*	0.071

*Mean (SD), **Median (IQR), TDF- Tenofovir, AZT- Zidovudine

4.5.4. Change in Glomerular Filtration Rate

Serum creatinine levels were available in 121 (73.8%), 73 (44.5%), and 35 (22.0%) in TDF and 30(50.8%), 15(23.4%) and 12(21.0%) in AZT groups at 6, 12 and 24 months of follow up respectively. In TDF group the median (IQR) estimated GFR levels were 112.35 (38.29), 109.56 (38.28) ml/min at 6 and 12 months respectively. On the other hand, the median (IQR) estimated GFR levels were 105.74(30.76) and 104.71 (33.9) ml/min at 6 and 12 months respectively in AZT group. At the end of follow up (2 years) the mean (SD) estimated GFR levels were 107.8 (32.62) and 116.44 (25.5) ml/min in TDF and AZT groups respectively.

The change in estimated GFR at 6 and 12 months of follow up showed significant reduction from baseline in TDF group; however the change in estimated GFR at 24 months of follow up didn't show statistically significant difference between TDF and AZT groups (Table 6).

Table 6: Change in estimated Glomerular filtration rate in Patients Started Antiretroviral Therapy in Tenofovir and Zidovudine based regimens from August 31, 2010 to August, 31, 2013 at Zewditu Memorial Hospital

	TDF group	AZT group	P value
6 month	-0.06 (21)**	1.47 (6)**	0.009
12 month	-1.87 (31.0)**	13.01 (29.0)**	0.001
24 month	-14.37 (9.28)*	12.69 (7.73)*	0.109

*Mean (SD), **Median (IQR), TDF- Tenofovir, AZT- Zidovudine

4.6. Mortality and program failure in TDF and AZT groups

In TDF group the estimated cumulative mortality was 6%, 9%, 9% and 9% at 6, 12, 18 and 24 months respectively. In AZT group the estimated mortality was 9%, 13%, 13%, and 13% at 6, 12, 18, and 24 months respectively (Table 7). On the other hand, the cumulative program failure in TDF group was 12%, 19%, 24% and 28% at 6, 12, 18 and 24 respectively and in AZT group it was 12%, 28%, 28% and 28% at 6, 12, 18 and 24 months respectively (Table 8).

Table 7: Estimates of cumulative death in patients started on Tenofovir and Zidovudine based antiretroviral therapy from August 31, 2010 to August 31, 2013 at ZMH

Regimen category	Interval start time (month)	Number entering interval	Number of deaths	Cumulative proportion of survival at the end of interval
TDF	0	164	10	0.94
	6	137	3	0.91
	12	125	0	0.91
	18	114	1	0.91
	24	101	0	0.91
AZT	0	59	5	0.91
	6	47	2	0.87
	12	36	0	0.87
	18	34	0	0.87
	24	34	0	0.87

TDF- Tenofovir, AZT- Zidovudine, n=223

Table 8: Estimates of cumulative program failure in patients started on Tenofovir and Zidovudine based regimens from August 31, 2010 to August, 31, 2013 Zewditu Memorial Hospital

Regimen category	Interval start time (month)	Number entering interval	Number of lost to follow ups	Cumulative proportion of survival at the end of interval
TDF	0	164	20	0.88
	6	137	10	0.81
	12	125	7	0.76
	18	114	7	0.72
	24	101	0	0.72
AZT	0	59	7	0.88
	6	47	8	0.72
	12	36	0	0.72
	18	34	0	0.72
	24	34	0	0.72

TDF- Tenofovir, AZT- Zidovudine, n=223

When expressed in person-time, the overall rate of mortality for the cohort was 6.38 deaths per 100 PYRs (CI 95%: 2.55-15.65). In patients on TDF based regimens the rate of mortality was 5.6 death per 100 PYRs (CI 95%: 3.06-9.39) compared with 8.86 death per 100 PYRs (CI 95%: 3.55-18.26) in those patients on AZT based regimens. The mean time to death was 676.82 days [95% CI (649.56 – 704.07)] and 651.06 days [95% CI (596.25 – 705.86)] for TDF and AZT groups respectively. The time to death between the two cohort groups did not show statistically significant difference p=0.426 (Fig. 5). On the other hand the mean time to program failure was 597.99 days [95% CI (561.57 – 634.42)] and 570.8 days [95% CI (501.61 – 639.99)] for TDF and AZT based regimens respectively (p=0.876).

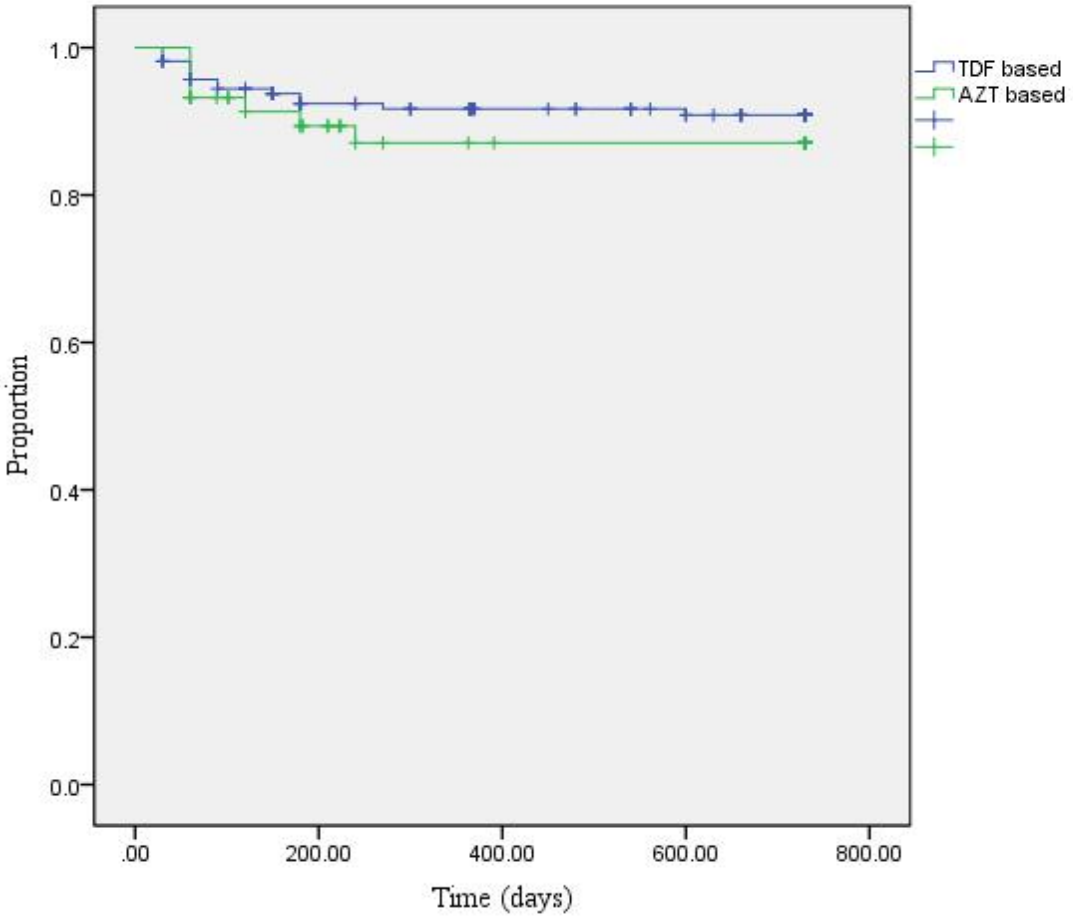

Fig. 5: Survival estimate for mortality in patients initiated on Tenofovir and Zidovudine based regimens at Zewditu Memorial Hospital from August 31, 2010 to august, 31, 2013

4.7. Association between Mortality and Treatment Groups

Bi-variable Cox regression was done to identify variables for multivariable Cox regression. Therefore, in bi-variable Cox regression analysis age, sex, baseline estimated GFR, CD4 count, OIs, WHO stage, weight, TB treatment, and NNRTIs were associated with mortality ($p < 0.25$). These variables were retained in multivariable Cox regression model in addition to the NRTI groups. The hazard for mortality among TDF and AZT groups didn't show statistically significant difference (Table 9).

Table 9: Crude and adjusted Cox proportional hazard regression for predictors of mortality in patients in Patients Started Tenofovir and Zidovudine based regimens from August 31, 2010 to August 31, 2010 at zewditu memorial hospital

Variables	CHR (95% CI)	P value	AHR (95% CI)	P value
TDF based	1	0.443	1	0.188
AZT based	1.4 (0.58-3.57)		2.1(0.7-6.36)	

Analysis adjusted for sex, age, baseline CD4 count, GFR, hemoglobin, body weight, WHO stage, NNRTIs, TB treatment, OIs TDF-Tenofovir, AZT- Zidovudine, ART- Antiretroviral therapy, CHD- Crude hazard rate, AHR- Adjusted hazard rate, GFR- Glomerular filtration rate, WHO- World health organization, NNRTIs- Non-nucleotide reverse transcriptase inhibitors, TB- Tuberculosis, OIs- Opportunistic infections, SD- Standard deviation

4.8. Immunological Outcome

4.8.1. Change in CD4 Count

CD4 count measurements were available in 127 (77.4%), 107 (65.2%), 70 (42.7%) and 37(62.7%), 33(55.9%), 24(40.7%) at 6, 12 and 24 months in TDF and AZT groups respectively. The median (IQR) CD4 counts at 6 and 12 months were 205 (165) and 266 (202) cells/mm3 in TDF and 247 (106) and 273 (167) cells/mm3 in AZT groups respectively. At the end of follow up (2 years) the mean (SD) CD4 counts were 414.47 (208.54) and 387.54 (144.12) cells/mm3 in TDF and AZT groups respectively. The changes in CD4 count at 6, 12 and 24 months of follow up showed no statistically significant difference between TDF and AZT groups (Table 10).

Table 10: Change in CD4 Count in Patients Started Tenofovir and Zidovudine based regimens from August 31, 2010 to August, 31, 2013 at Zewditu Memorial Hospital

	TDF group	AZT group	P value
6 month	69 (126)**	72 (84)**	0.492
12 month	113 (160)**	160 (129)**	0.883
24 month	246.94 (22.3)*	211.88 (29.71)*	0.405

*mean (SD), ** Median (IQR), TDF- Tenofovir, AZT- Zidovudine

5. Discussion

This study was carried out to compare the safety and effectiveness of first-line ART in HIV patients taking TDF and AZT based regimens. The study participants were stratified in TDF and AZT groups. The comparison of subjects was made in terms of CD4 count, estimated GFR, hemoglobin, OIs, WHO clinical stage, pregnancy, TB treatment, OIs prophylaxis, weight and concomitant chronic diseases.

The two cohort groups were similar with baseline clinical characteristics such as CD4 count, OIs, pregnancy, WHO clinical stage, concomitant chronic disease and OIs prophylaxis. However, significant difference was observed in terms baseline TB treatment. The initiation of more patients with EFV based NNRTI in TDF group may be the reason for this difference, as NVP is contraindicated during TB treatment. The laboratory monitoring parameters, baseline estimated GFR and hemoglobin also differed significantly across the two treatment groups. Majority of patients with high baseline hemoglobin were started on AZT based regimens, whereas those patients with high baseline estimated GFR were started on TDF based regimens. This might be due to prescribers' preference in regimen selection based on the potential risks of anemia and renal toxicities in patients taking AZT and TDF respectively.

In this study more patients (61.9%) were started on TDF/3TC/EFV regimen, as the recent WHO recommendation for the use of ART regimens in resource limited areas. Since the introduction of TDF in resource limited areas, its use has been increasing as part of first-line ART for the treatment of HIV. ART is characterized by different rates of responses and ADRs, therefore comparing the regimens in different populations and methods is essential. Most of the studies in resource limited areas compared TDF with the previous first-line NRTIs, d4T and/or AZT. In this study patients on TDF and AZT based first-line ARVs were compared.

Time to toxicity driven regimen substitution varied depending on the NRTI used in first-line ART, with AZT occurring early after treatment initiation. This can be explained by the occurrence of anemia during the first 6 month of treatment, which is the major ADR of AZT (Hassan et al., 2009). In this study, shorter time to toxicity driven regimen substitution was observed in AZT than TDF group. The mean time before toxicity driven regimen substitution was (718.26 days) in TDF compared to AZT group (641.83 days). This finding is consistent with the result obtained from Zimbabwe, which showed longer mean time before toxicity driven

regimen substitution in TDF (618 days) compared to AZT group (388 days) (Mudzuviti et al.,2015). On the other hand, a study in South Africa obtained shorter median time before toxicity driven regimen substitution in TDF group (1.5 years) than AZT (2 years) (Njuguna et al., 2013). The possible reason for this difference could be the variability in follow up durations between the cohorts groups in the South African study (Njuguna et al., 2013), in which only 2 years data were reviewed for participants in TDF group compare to 9 years in AZT group.

In this study the rate of toxicity driven regimen substitution in AZT was significantly higher than TDF. Other studies in South Africa (Velen et al., 2013; Brennan et al., 2013; Njuguna et al., 2013), Zambia (Chi et al., 2010), Lesotho (Bygrave et al., 2011) reported similar findings. In addition to this, other studies in India (Thuppal et al., 2015) and east Africa (Macharia et al., 2014) reported higher proportion of toxicity driven regimen substitution in AZT than TDF group. In the adjusted Cox regression model, toxicity driven regimen substitution was 5 times higher in AZT than TDF group. This result is consistent with the results obtained from South Africa, Lesotho, and Zambia, which showed 5.2, 2.8, 2.23 and 2.74 fold higher risk of toxicity driven regimen substitution in AZT than TDF (Velen et al., 2013; Brennan et al., 2013; Bygrave et al., 2011; Chi et al., 2010). And also in South Africa, patients started on TDF based regimens showed 65% reduction in single drug substitution as compared to patients on AZT based regimens (Njuguna et al., 2013). The varying length of follow up durations across the studies may be the reason for the different hazards of toxicity related regimen substitution in the studies. In the present study, the mean follow up times for TDF and AZT groups were 555.54 and 489.24 days, respectively. In the other studies, the median durations of follow up in TDF and AZT groups were 208 and 308 days in Zambia (Chi et al., 2010), 483 and 493 days in Lesotho (Bygrave et al., 2011), 1.6 and 3.1 years in South Africa (Brennan et al., 2013), respectively.

The median change in estimated GFR at 6 and12 months were significantly lower in TDF (-0.06 and -1.87 ml/min respectively) than AZT (1.47 and 13.01 ml/min respectively). However, the mean change in estimated GFR at 24 months of follow up showed no statistically significant difference between the cohort groups. This is similar to the results of other studies by (Horberg et al., 2010; Pozniak et al., 2006), in which significantly lower change in GFR were obtained in patients treated with TDF based regimens. The result of the present study is different from the result obtained in Zambia (Chi et al., 2010), in which no statistically significant difference was

reported in TDF and AZT groups at 6 and 12 months of follow up. The higher number of missing values in the studies probably contributed to this difference.

In the present study, mortality occurred during the first six months of follow up in both groups and it was constant during the rest of follow up time. However, loss to follow up varied depending on the NRTI used in first-line ART, with AZT occurring early after treatment initiation and at a higher rate later on in follow up amongst patients on TDF. The overall loss to follow up was high in this study, similar to other ART programs in Africa (Chi et al., 2010, Odafe et al., 2012, Appolo et al., 2014). The high rate of loss to follow up can be due to incomplete ascertainment of mortality. The reasons for follow up losses were not investigated in the present study, but a study in Uganda suggested that majority of patients reported as loss to follow up may have actually died (Geng et al., 2010). The time to both mortality and program failure were similar in the two cohort groups. Similar findings were obtained in studies from Ethiopia (Ayele et al., 2017), Zambia (Chi et al., 2010), South Africa (Njuguna et al., 2013).

In the adjusted Cox regression model, mortality was similar in the two cohort groups. This is similar to other findings obtained from studies in Ethiopia (Ayele et al., 2017), Zambia (Chi et al., 2010), South Africa (Njuguna et al., 2013) and Lesotho (Bygrave et al., 2011). On the other hand, higher risk of mortality in TDF than AZT group was obtained in Uganda (Asiimwel et al., 2016), and in Nigeria (Eguzo et al., 2014; Odafe et al., 2012). Unlike the finding of this study, the study in South Africa reported higher risk of mortality in AZT than TDF group (Velen et al., 2013). These discrepancies could be due to differences in mortality outcome definitions between the studies. Some of the mentioned studies used a composite end point, which comprised mortality and loss to follow up and withdrawal from the program in a single outcome variable.

The mean change in CD4 count at 6, 12 and 24 months were similar in TDF and AZT groups. Similar results were obtained from studies in Eritrea (Medhanie et al., 2015), India (Gaikwad et al., 2015; Hemasri et al., 2016; Thuppal et al., 2015). On the other hand, studies in Ethiopia (Ayele et al., 2017), and South Africa (Velen et al., 2013) reported better immunological response in TDF than AZT group. The possible reason for this difference is likely the initiation of more patients with considerably better health status in AZT as compared to TDF group in the present study.

6. Limitations of the Study

Cohort study designs are one of best options to perform comparative observational studies; however, use of data from routine service delivery programs also has limitation due to missing data. For example, data on suspected ADRs was incomplete in this study, thus substitution of NRTI was used to indicate the possible source of ADR. In addition, the missing follow up CD4 count, hemoglobin, and estimated GFR values might influence the apparent difference in the cohort groups. The small sample size is also another limitation of the study. In this study, virological outcome was not assessed due to unavailability of routine viral load monitoring during the study period in this setting. Hence this could be the other limitation of the study. Finally, adherence wasn't assessed in this study; hence this could be the other drawback of this study.

7. Conclusion

In this study, TDF based regimens have shown superior safety with less toxicity driven regimen substitution and longer duration before toxicity driven regimen substitution. There was no significant difference in mortality and change in CD4 count between the two cohort groups. However, the values of estimated GFR at 6 and 12 months of follow up showed significant reduction in patients taking TDF based regimens.

To the recent knowledge, this is the first study to compare TDF and AZT based regimens regarding toxicity related regimen substitution after the introduction of TDF as first-line ARV in Ethiopia. In this study TDF based regimens showed superior safety (tolerability) and similar effectiveness as AZT based regimens. The findings of this study support the WHO recommendations on the use of TDF as preferred first-line ART regimen in resource limited settings.

8. Recommendations

Tenofovir (TDF) use as preferred first-line ART in resource limited settings is recommended by WHO. It is also included in the 2014 Ethiopian national consolidate ART guideline as preferred first-line ART. Based on the findings of this study, the following recommendations are forwarded

- The better tolerability profile of TDF is advantageous in resource limited areas to reduce the overall medical cost of patients. Therefore, the increase in the use of TDF as part of first-line agent should be continued.
- Health providers should perform routine renal function monitoring in patients taking TDF.
- Further research is needed to compare virological effectiveness of TDF and AZT based ART regimens. .

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10. Annex

Data abstraction form

SECTION 1- Patient Demographics

Patient code……..

ART unique number…….

Patients registration number……

Sex *Male* ☐ *Female* ☐

Age at ART initiation……..

Marital status *never married* ☐ *Married* ☐ *Divorced* ☐ *Widowed* ☐

Date of ART initiation……

Educational status *no education* ☐ *Primary school* ☐

Secondary school ☐ *Higher institution* ☐

SECTION 2- Baseline Clinical Characteristics and Laboratory Values

CD4 count……

Serum creatinine (SrCr)……..

Hemoglobin (Hgb)……

Body weight…….

Height……..

Body mass index (BMI)…….

Pregnancy (for women) ☐ *No* *yes* ☐

OIs O *PCP* ☐ETB ☐ *TB* ☐ *Toxoplasmosis* ☐

Other (specify) …….

WHO clinical stage I. ☐ ☐ III. ☐ *IV*. ☐

Concomitant chronic diseases

DMHTN ☐ ☐ *HBV* Renal diseases ☐ ☐

CVD ☐ Others (specify)……

OIs prophylaxis *Cotrimoxazole* ☐ *Isoniazid* ☐ dapson ☐

Anti TB medications *Yes* ☐ *No* ☐

If yes specify TB medications…….

Chronic care medications (drug name, dose, frequency)……

Other medications (drug name, dose, frequency, duration)……

Drug allergy *Yes* *No* ☐ ☐

If yes specify the type and responsible drug …….

Follow-up information

OIs *yes* ☐ *No* ☐

If yes specify the OI……

The date OI diagnosed……..

Other concomitant diseases *yes* ☐ *No* ☐

If yes specify the disease……

Other medications …….

Drug substitution *Yes* ☐ *No* ☐

Specify the drug substituted……..

Specify the date of drug substitution……

Discontinuation *yes* ☐ *No* ☐

If yes reason for discontinuation *Loss to follow-up* ☐ *Death* ☐

Transferred out ☐

Other (specify)……

Date of discontinuation……

1. **CD-4 count**
   6 month……. 18 month…….
   12 month……. 24 month……..
2. **SCr. Values**
   6 month……. 18 month…….
   12 month……. 24 month……..
3. **Hgb. Values**
   6 month……. 18 month…….
   12 month……. 24 month……..
4. **Body weight (BMI)**
   6 month……. 18 month…….
   12 month……. 24 month……..
5. **WHO clinical stage**
   6 month……. 18 month…….
   12 month……. 24 month……..