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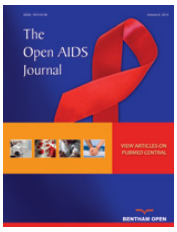

RESEARCH ARTICLE

Clinical Outcomes of Tenofovir *Versus* Zidovudine-based Regimens Among People Living with HIV/AIDS: a Two Years Retrospective Cohort Study

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Abstract:

Background:

Tenofovir (TDF) based regimen is one of the first line agents that has been utilized routinely since 2013 in Ethiopia. Unfortunately, there is limited information regarding the Clinical outcomes and associated risk factors in this setting, where patients generally present late, have high rates of TB and other infectious conditions.

Methods:

A two year retrospective cohort study was conducted from February 10/2015 to March 10/2015 at Jimma University Specialized Hospital. A total of 280 records were reviewed by including data from September 3, 2012 to July 31, 2014. Records were selected using a simple random sampling technique. Data was collected on socio-demographic, clinical and drug related variables. Data was analyzed using STATA 13.1. Kaplan-Meier and Cox regression were used to compare survival experience and identify independent predictors. Propensity score matching analysis was conducted to elucidate the average treatment effects of each regimen over opportunistic infections.

Results:

Of 280 patients, 183(65.36%) were females and 93(33.32%) of females belong to Tenofovir group. Through 24 months analysis, TDF based regimen had a protective effect against death and opportunistic infections (OIs), (AHR=0.79, 95% CI [0.24, 2.62]) and (AHR=0.78, 95%CI [0.43, 1.4] respectively. The average treatment effect of TDF/3TC/EFV was (-71/1000, p=0.026), while it was (+114/1000, *p=0.049*) for AZT/3TC/EFV. However, TDF/3TC/NVP was associated with statistically insignificant morbidity reduction (-74/1000, *p=0.377*). Those with body mass-index (BMI) <18.5kg/m2 (AHR=3.21, 95%CI [0.93, 11.97]) had higher hazard of death. Absence of baseline prophylaxis (AHR=8.22, 95% CI [1.7, 39.77]), Cotrimoxazole prophylaxis alone (AHR=6.15, 95% CI [1.47, 26.67]) and BMI<18.5kg/m2 (AHR=2.06, 95% CI [1.14, 3.73]) had higher hazards of OIs.

Conclusion:

The survival benefit of TDF based regimen was similar to AZT based regimen and therefore can be used as an alternative for HIV/AIDS patients in resource limited setups. However, since this study was not dealt with toxicity of the regimens, we recommend to conduct high quality design on this issue.

Keywords: Jimma University Specialize hospital, Tenofovir regimen, Treatment outcomes, Zidovudine regimen.

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INTRODUCTION

Emergence of Acquired immunodeficiency syndrome (AIDS) around 1980's, as a major public health threat leads to the introduction of potent ART. This had resulted in dramatical reduction of associated mortality, morbidity, improved quality of life,and revitalized communities [1, 2]. Before 2009, the most commonly used backbone drug in resource-limited settings was either Zidovudine (ZDV) or stavudine (D4T), which had a high rate of side-effects [3]. These side-effects have led to banning of stavudine in developed countries in favor of less toxic longer half-life, and more friendly alternatives like tenofovir disoproxil fumarate (TDF)[4 - 6]. Randomized clinical trials have demonstrated comparable or greater efficacy of TDF compared with ZDV or D4T [7 - 12] in combination therapy with regards to virological suppression, as well as a tendency for less toxicity-related discontinuations and improved adherence in both developed and resource limited settings [8 - 13]. Nevertheless, most of these RCTs were about efficacy of TDF in combination therapy on virological suppression and/or immunological boosting. The effect of TDF on survival benefits and factors influencing mortality and morbidity in low income nations are rarely exploited. The 2009 World Health Organization (WHO) guidelines for ART recommended the phasing out of stavudine in resource-limited settings and many African countries adapted this recommendation and revised their guidelines in which the first line regimen consisted of either AZT or TDF backbone [14].

TDF become routinely utilized in the current practice setup since the beginning of 2013 in Ethiopia. Despite, its efficacy and safety issues are unknown in an Ethiopian setting where patients generally present late, have high rates of TB and other infectious conditions [15]. As most studies are from high income settings and extrapolation might not scientifically sound,evidences through research addressing questions regarding the optimum first-line ART regimen in patients living with HIV in low income countries are necessary. There are conflicting results coming out of the current literatures regarding efficacy and safety of TDF based regimens compared with AZT based regimen. For instance, a body of literatures reported that TDF+3TC+NVP was associated with higher hazard of mortality and virologic failure when compared to ZDV +3TC+NVP [16, 17] and even TDF based regimens were less protective than AZT based regimens in HIV patients living in resource limited settings [18]. A systematic review showed that the overall mortality rate between patients who were taking either AZT or TDF based ART regimens was not significantly different [19]. On the other hand, studies reported that TDF performed better than either d4T or AZT, most notably with less drug substitution and mortality [20, 21]. Serious renal toxicity, like acute renal failure requiring dialysis, progressive decline in renal function, proximal renal tubular dysfunction, and Fanconi-syndrome were also reported by some literatures [17, 18, 22, 23]. In another study, patients given tenofovir containing regimens experienced renal stability or improvement, even if they had pre-existing mild to moderate renal dysfunction [24].

Taking together, these inconclusive results and considering the different nature of the study setting, it is important to explore the mortality and morbidity benefits of TDF and associated factors. Therefore, this study compared AZT and TDF based first line regimens in terms of their clinical effects and associated risk factors in Ethiopia, one of the low-income countries.

METHOD AND PARTICIPANTS

Study Area and Period

The study was conducted at Jimma University specialized Hospital, which is located in Jimma town; Jimma Zone, Oromia Region, Southwest Ethiopia and is about 346km far away from Addis Ababa. The hospital has ART clinic with about 7,486 clients. The ART clinic services involve HIV care and treatment, TB treatment, post exposure prophylaxis service and prevention of mother to child transmission services. The study was conducted from February10, 2015 to May 10, 2015 by including data from September 2012 to July 2014.

Study Design and Inclusion Criteria

A retrospective hospital based cohort study was conducted on adult patients who were on TDF and ZDV based regimens between September 2012 and July 2014 that fulfil inclusion criteria. The study was conducted by dividing the total sample in two major classes as TDF group and AZT group which intern further classified as TDF/3TC/ EFV or NVP, (TDF based regimen) and AZT/3TC/NVP or EFV (AZT based regimen).

Patients on AZT and TDF based first line regimens, having at least six months of follow-up, whose records were legible and complete, who have CD4 count at least at base line and six months and older than 14 years (as ages > 14 years old patients are considered adults & receive adult formulations of ART regimen in this setup), included in the

study. Those transferred out within < 6months of follow up, pregnant women and patients with incomplete records were excluded.

Sample Size and Sampling Techniques

Sample size determination was guided by the number of patients on TDF/3TC/NVP, whereby only 70 patients fulfil the inclusion criteria and included into the study. Patients from the other regimens were selected based on the above figure to make the AZT to TDF group ratio 1:1. Therefore, frequency matching was used so select a total of 280 subjects, with 140 charts of patients from each group were reviewed (Fig. **1**). TDF groups (n_1 = 140) were those initiated with TDF based regimen which were identified from patient charts of hospital records. A simple random sampling technique was used to select patient charts from each regimens using computer generated random number. One from TDF exposed patient was selected for one patient exposed to AZT, resulting in 140 total patients (n_2 = 140), which were selected by similar manner as TDF group.

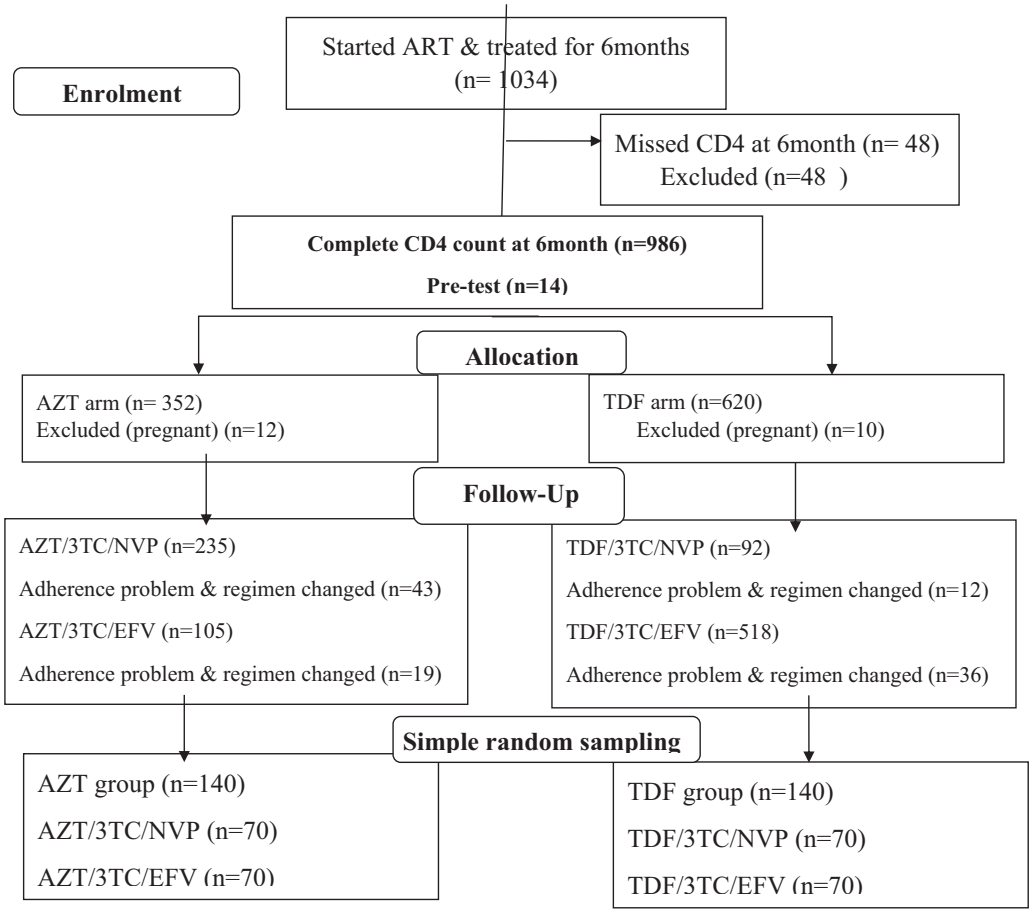


Fig. (1). Sample recruitment chart at JUSH; of patients attending ART clinic, February10 -March10, 2015.

Data Collection Procdures and Analysis

Data on demographic, clinical, laboratory, drug administered, comorbidities and adherence was collected by record review using English version checklist which was prepared after reviewing different relevant literatures. Baseline body mass-index of the subjects was latter calculated after collection of baseline height and weight of the patient from patents chart. Data from antiretroviral drugs and patient information sheet was collected by pharmacists and data from ART clinic intake form, HIV care/ART follow up and patient sheet was collected by the nurses.

Data was entered into Epi-Data twice and exported to STATA 13.1 for cleaning and analysis. Descriptive analysis was performed and results were presented by text, tables and charts. Kaplan-Meier (log rank test) was used to compare baseline characteristics of the patients. For dichotomous variable such as death, chi-square test was performed to check adequacy of cells before performing Cox regression. Cox regression model assumption of proportional hazards was checked by testing an interaction of covariates with time. Bivariate Cox regression was performed to identify candidate

variables for multivariable Cox regressions. Variables with p-value ≤ 0.25 in bivariate regression were considered as candidates for multivariable regression. Multivariable Cox regression was performed using Forward Wald method to identify independent predictors of treatment outcome. Hazard ratio with 95% confidence intervals was used as measure of strength of association and p-value < 0.05 was considered to declare a statistical significance. Finally a matching estimator, propensity score matching was conducted to show the opportunistic infection reduction capacity of each regimen considering AZT/3TC/NVP as a reference regimen. This is a better analysis method to show the true result of the intervention. It is a matching technique (estimator) that uses the idea of randomized controlled studies in which the impact of confounding variables are minimized.

RESULTS

A total of 1034 patients started antiretroviral therapy (ART) and treated for 6months. Of which 352 belonged to AZT arm, 620 were from TDF arm who have complete CD4+ count at 6month of treatment. Forty eight patients were excluded initially from either regimens due to missed CD4+ count at 6month, 22(12 and 10 from AZT and TDF) because of pregnancy and 110 patients due to regimen change and adherence issue (Fig. **1**).

The overall analysis time at risk was 539.39 years. The cohort contributed to a total of 2.74/100 and 2.72/100 person-years of follow-up for TDF and AZT groups respectively. The mean + standard deviation (SD) duration of follow up was 714.2 + 69.6 and 708.8 + 78.9 days (*p=0.753*) among TDF and AZT, respectively. Study participants retained in the cohort for different lengths of follow up time: stayed for a minimum of 7.4 and 8.9 months for TDF and AZT groups, respectively (*p=0.743*).

Descriptive Analysis of Baseline Characteristics

The mean + SD age of the study participants was 32.3 + 7.4 and 32.3 + 9.2 years for TDF and AZT groups, respectively (p=0.196). The mean + SD baseline body mass index (BMI) was 19.7 + 3.4 and 20.4 + 3.0kg/m^2 respectively (p=0.075).

Comparative baseline characteristics of the study subjects is described in Table **1**. Majority of the study subjects 183 (65.36%) were females with relatively equal distribution among the groups, 90 (64.3%) *versus* 93(66.4%), respectively. At baseline, the mean + SD CD4 count was 164.64 + 83.36 and 175.21 + 89.14 cells/mm^3 for TDF and AZT groups, respectively (p=0.029).

Table 1. Comparative baseline characteristics of the study cohort at JUSH, February 10 - March 10, 2015.

All n=280 Variables	TDF group (n=140)	AZT group (n=140)	p-value
Sex			
Male	50(35.7)	47(33.6)	0.706
Female	90(64.3)	93(66.4)	
Age			
<25	27(19.3)	32(25.9)	0.196
26-45	108(77.1)	98(85.9)	
>45	5(3.6)	10(7.2)	
BMI			
<18.5	52(37.1)	37(26.4)	0.075
≥18.5	88(62.9)	93(73.6)	
Educational level			
Illiterate	22(15.8)	30(21.4)	0.089
Primary	48(34.2)	58(41.4)	
Post-primary	70(50)	52(37.2)	
Residence			
Urban	97(69.3)	110(78.5)	0.13
Rural	43(30.7)	30(21.5)	
Occupation			
Employed	68(48.6)	58(41.5)	0.296
Unemployed	46(22.8)	55(39.2)	
Housewife	26(18.6)	27(19.3)	
Religion			
Orthodox	59(42.1)	80(57.1)	0.01
Muslim	45(32.1)	42(30)	
Others	36(25.8)	18(12.9)	

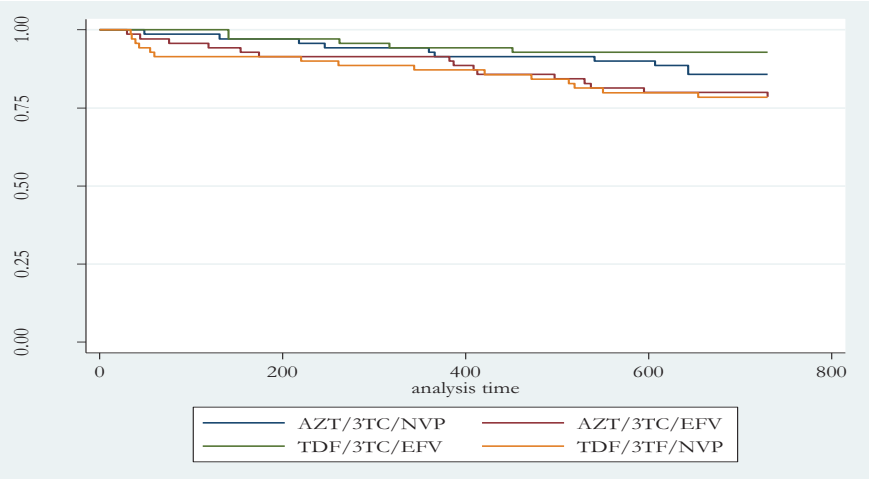
(Table 1) contd.....

All n=280 **Variables**	**TDF group (n=140)**	**AZT group (n=140)**	**p-value**
Marital status			
Single	76(54.3)	77(55.0)	0.207
Married	23(16.5)	29(20.7)	
Divorced	33(23.5)	21(15.1)	
Widowed	8(5.7)	13(9.2)	
Alcohol			
No	113(80.7)	102(72.9)	0.119
Yes	27(19.3)	38(27.1)	
BaselineCD4+count			
(Mean ± SD)	164.64 ± 83.36	175.21 ± 89.14	**0.029**
<200	92(65.7)	74(53.9)	
≥200	48(34.3)	66(47.1)	
WHO stage			
I	32(22.9)	36(25.7)	0.928
II	46(32.9)	47(33.6)	
III	47(33.6)	43(30.7)	
IV	15(10.6)	14(10)	
Functional status			
W	110(78.6)	79(56.4)	0.000
A	24(17.1)	56(40.0)	
B	6(4.3)	5(3.6)	
TB(treatment)			
No	120(84.7)	113(87.9)	0.597
Yes	20(15.3)	17(12.1)	
Prophylaxis			
CPT+ INH	37(26.4)	30(21.5)	0.231
CPT alone	86(61.4)	99(70.7)	
Neither	17(12.2)	11(7.8)	

BMI-body mass index, OIs-opportunistic infections, CPT-cotrimoxazole, INH-Isoniazid, TB-Tuberculosis, TDF-Tenofovir, AZT-Zidovudine, WHO-World health organization, CD4-cluster of differentiation, SD-Standard deviation

Efficacy: Clinical Outcomes

The proportion of death among TDF and AZT group was 3.68% and 4.48% (*p=0.759*). The survival time was, (mean + SD), 713.46 + 4.411 and 709.57 + 4.983 days (*p= 0.743*) respectively. When the proportion of death is stratified among individual regimens as compared to AZT/3TC/NVP, TDF/3TC/EFV based regimen carries the lowest proportion 2(2.9%); and it was almost similar *i.e.* 3(4.44%), for the rest of the regimens. The proportion of opportunistic infection was 14.3%and 17.9% (p=0.228), respectively among TDF and AZT groups. The mean + SD survival time to opportunistic infection was 656.574 + 14.58 and 654.793 + 14.339 days, respectively (p=0.462). Patients exposed to TDF/3TC/EFV had favorable survival experience; and the difference was marginally significant as shown by the Kaplan-Meier survival estimate (Fig. **2**).



Log-rank p=0.063

Fig. (2). Survival estimates for opportunistic infections among the cohort at JUSH, from February 10 to March 2015.

Predictors of Clinical Outcomes

The survival experience among the groups was compared by log-rank test. Baseline CD4+ count,sex and BMI were predictors for death on bivariate cox-regression (p<0.11). Therefore, after adjusting for other variables (Table **2**), patients with baseline body mass index of below normal (<18.5) were found to be at increased risk of death (AHR=2.21, 95%CI [1.93, 11.97], *p=0.049*). On the contrary, a unit increment in baseline CD4+ count was found to decrease the risk of death by 18% (AHR=0.82, 95%CI [0.809, 0.998], p=0.019).

Table 2. Crude and adjusted cox-proportional hazard regression for predictors of death of the cohort at JUSH, February 10 to March 10, 2015.

Variables	CHR [95%CI]	p-value	AHR [95%CI]	p-value
Sex				
Male	1	0.10	**1**	**0.084**
Female	5.6 [0.71,43.5]		**6.14[0.78,48.34]**	
Age				
≤25	2.4[0.69,8.65]	0.167		
26-45	1	0.455		
>45	2.3[0.27,18.6]			
BMI				
<18.5	3.4[1.05,11.25]	0.042	**2.21[1.93, 11.97]**	**0.049**
≥18.5	1		**1**	
Educational level				
Illiterate	1.35[0.23,8.08]	0.75		
Primary	1	0.44		
Post-primary	1.73[0.43,6.93]			
Residence				
Urban	1	0.42		
Rural	1.66[0.49,5.69]			
Religion				
Orthodox	1	0.55		
Muslims	0.66[0.17,2.55]	0.33		
Others	0.35[0.04,2.87]			
Occupation				
Employed	1	0.83		
unemployed	0.87[0.25,3.09]	0.38		
Housewife	0.39[0.05,3.21]			
Marital status				
Married	1	0.35		
Single	1.98[0.48,8.27]	0.60		
Widowed	0.56[0.07, 4.79]	0.204		
Divorced	2.89[0.56, 14.92]			
Alcohol				
No	1	0.803		
Yes	1.18[0.31,4.46]			
Baseline CD4+ count	**0.89[0.981,0.998]**	**0.017**	**0.82[0.809,0.998]**	**0.019**
WHO staging				
I	1	0.488		
II	1.79[0.35,9.2]	0.76		
III	0.74[0.10,5.2]	0.375		
IV	2.43[0.34,17.23]			
TB (treatment)				
No	1.49[0.19,11.67]	0.702		
Yes	1			
Regimen				
TDF group	**0.83 [0.25,2.71]**	**0.753**	**0.67[0.2,2.24]**	**0.52**
AZT group	**1**		**1**	
Prophylaxis	1			
CPT + INH	1.27[0.26,6.11]	1		
CPT	2.5[0.35,17.77]	0.75		
Neither		0.359		

BMI-body mass-index, AHR-adjusted hazard ratio, CHR-cumulative hazard ratio, INH-isoniazid, TB-tuberculosis, TDF-Tenofovir, AZT-Zidovudine, CPT-Cotrimoxazole prevent therapy

Patients on AZT based regimen had 33% higher risk of death than their TDF based regimen counter parts (AHR=

0.67, 95% CI [0.20, 2.40], *p=0.52*), but the difference lacked statistical significance.

Similarly, log-rank test was performed to compare their survival experience for opportunistic infections among the groups and bivariate and multivariate cox- regression analysis was conducted and the result was presented in Table **3**.

Table 3. Crude and adjusted cox-proportional regression analysis for predictors of OIs at JUSH, from February 10 to March 10, 2015.

Variables	CHR [95%CI]	p-value	AHR[95%CI]	p-value
Sex				
Male	1	0.398		
Female	1.32[0.69,2.52]			
Age				
<25	1.26[0.634,2.494]	0.502		
26-45	1	0.827		
>45	0.85[0.64,2.51]			
BMI				
<18.5	2.18 [1,3.24]	0.009	**2.05[1.13,3.73]**	**0.018**
≥18.5	1		**1**	
Educational level				
Illiterate	1.02[0.53,1.96]	0.729		
Primary	1.15[0.52,2.54]	0.995		
Post-primary	1			
Area of residence				
Urban	1	0.098	**1**	**0.08**
Rural	1.97[0.88,4.12]		**1.4[0.21,1.09]**	
Occupation				
Employed	1.28[0.69,2.39]	1		
Unemployed	0.57[0.21,1.51]	0.421		
Housewife		0.259		
Marital status				
Single	1	0.168		
Married	1.67[0.804,3.50]	0.268		
Divorced	1.54[0.719,3.28]	0.447		
Widowed	1.52[0.52,4.44]			
Religion				
Orthodox	1	0.51		
Muslim	0.86[0.7,2.68]	0.44		
Others	0.49[0.14,3.87],			
Alcohol				
No	1	0.101	**0.48[0.20,1.14]**	**0.095**
Yes	0.49[0.21,1.15],			
Baseline CD4+ count				
	0.56[0.36,1.003]	0.058	**0.53[0.42,0.998]**	**0.039**
WHO stage				
I	1	0.758		
II	1.13[0.51,2.52]	0.720		
III	1.16[0.52,2.58]	0.697		
IV	1.24[0.42,3.62],			
TB(treatment)				
No	1	1.0		
Yes	1.0[0.42,2.36],			
Regimen				
TDF group	**0.8[0.45,1.44]**	**0.463**	**0.77[0.43,1.4]**	**0.405**
AZT group	**1**		**1**	
Prophylaxis				
CPT +INH				**0.013**
CPT alone	**1**	**0.006**	**1**	**0.009**
Neither	**7.12[1.71,29.57]**	**0.003**	**6.15[1.47,25.67],**	
	9.23[1.92,44.44]		**8.22[1.7,39.77],**	

BMI-body mass-index, AHR-adjusted hazard ratio, CHR-cumulative hazard ratio, INH-isoniazid, TB-tuberculosis, TDF-Tenofovir, AZT-Zidovudine, CPT-Cotrimoxazole prevent therapy

On multivariate cox-regression, patients with no baseline prophylaxis and those with baseline Cotrimoxazole only were found to be under higher risk of developing opportunistic infection (AHR=8.22, 95% CI [1.7, 39.77], *p=0.009*)

and (AHR=6.15, 95% CI [1.47, 25.67], p=*0.013)* respectively, regardless of the initial ART regimen they had commenced.

Also, those with low BMI (BMI<18.5kg/m^2) were almost two times at higher risk of developing opportunistic infections (AHR=2.05, 95% CI [1.13, 3.73], *p=0.018*). And a unit increment in baseline CD4+ count resulted in 47% reduction in the occurrence of OIs (AHR=0.53, 95% [0.42, 0.998**],** p=0.039). In addition, patients in AZT group, had 23% higher hazard of OIs than their TDF counterparts (AHR=0.77, 95% CI [0.43, 1.40], *p=0.405*), even though it was statistically insignificant.

On propensity score matching analysis, considering adherence and frequency of NNRTIs as a matching variables, occurrence of OI as an outcome variable, ART regimen as treatment dependent variable, and adjusting for all other potential confounders.

The average reduction of opportunistic infection among treated (Average treatment effect, ATET) with TDF based EFV regimen is -71/1000 (95% CI=-0.135, 0.008 *p=0.026).* However,AZT/EFV was associated with grater incidence of opportunistic infection relative to the base regimen, 0.114 (95% CI=0.001, 0.228, p=*0.049)* and TDF/NVP resulted in statistically insignificant reduction of OIs (Table **4**).

Table 4. Comparative opportunistic infection reduction capacity of different ART regimens at JUSH, from February 10 to March 10, 2015.

ART regimen**	Coefficient	AI Std. Err.	Z	p-value	95% CI
AZT/3TC/NVP	Base Regimen				
TDF/3TC/EFV	-0.071	0.032	-2.22	0.026	-0.135,0.008
AZT/3TC/EFV	0.114	0.058	1.97	0.049	0.001,0.228
TDF/3TC/NVP	-0.074	0.081	-0.88	0.377	-0.230,0.087

**Adjusted for all predictor variables among the TDF and AZT groups except variables that doesn't meet the criteria of propensity score matching analysis.so it is assumed that the TDF and AZT groups have the same distribution in confounder variables included in the model. For example, for AZT/3TC/EVF, all predictor variables for opportunistic infections and the base regimen is included in the model.

DISCUSSION

In this population with good adherence (adherence >95%)(52), a higher proportion of death was recorded among AZT groups (*p=0.759*). The survival time, of TDF was also shown improvement does not show any statistically significant difference (p= *0.743*).

Low body mass index (<18.5kg/m^2) at baseline and a unit increment in baseline CD4+ count was the independent predictors of death. Females and patients commencement AZT based regimen were also found to be at higher risk of death, although it was statistically insignificant .

A similar finding was reported by Damtew *et al*. [25], from Somali region, Karamara hospital. However, the proportion of death among patients groups was 29.8% and 31.9%(p=*0.429*), respectively in the previous study. The higher proportions of death might be due to smaller sample size (280 *vs*. 485 subjects), inclusion of patients only with good adherence, and exclusion of patients with follow-up less than six months, as most of the deaths occur within four months post initiation of ART [26]. Involvement of adherence supporters, improvement in the prophylactic and VCT services, might have played a role in reducing the incidence of death in current study.

The risk of death for patients with BMI<18.5Kg/m was more than two times higher, (p=0.049) compared to those with a BMI > 18.5 kg/m^2. In study from Malawi, individuals with BMI<16 kg/m^2 had six times higher risk of dying in the first three months than those with BMI>16 kg/m^2 [27]. *Asgaire et al*. [28] also estimated one year mortality nearly 50% among patients with severe malnutrition in Tanzania. In our finding, a unit increase in baseline CD4+ count, resulted in 18% risk of reduction in death (p=0.019). Study from USA [29] had also reported that in patients with higher baseline CD4+ counts(>200) the risk of death in the coming year was reduced to < 5%.The finding is also in accordance with the study conducted in South Africa [30] and Ethiopia [25].

Patients from AZT group had 33% higher hazard of death than their TDF exposed counter parts (p=0.52). Our finding is consistent with the study from South Africa where patients exposed to TDF based regimen had 40% lower risk of death than their AZT exposed counter parts (AHR=1.4 95% CI [1.3, 1.5] [20].

In our study, the overall prevalence of OIs in TDF and AZT group is 14.3% and 17.9%, respectively (p=0.496). The mean + SD survival time to opportunistic infection for TDF group was slightly improved (p=0.462). The average

treatment effect was favored TDF/3TC/EFV. History of baseline prophylaxis, baseline CD4+count and low base line body mass index (<18.5kg/m^2) were the independent predictors for the occurrence of OIs as identified by multivariate cox-regression. Although, it lacked statistical significance, patients randomized to AZT based regimen were 23% at higher risk of developing OIs.

This finding was concurrent with one Indian RCT in which slightly higher proportion of OIs was recorded in patients randomized to AZT group (46% *vs.* 31%, *p=0.22*) [31]. In addition to its 23% OIs risk reduction in our study, the slightly higher median survival time in TDF group may also explain the survival advantage of this regimen. A cohort study by *Samuel et al.* [32] conducted in Kenya indicated that patients commenced on TDF based have relatively higher mean survival than its AZT counterpart (*61 vs. 56.5 months*) respectively.

In addition, one extra opportunistic infection was prevented every 14 patients treated using this TDF/3TC/EFV regimen (p=*0.026*). On the contrary, AZT/3TC/EFV was the least protective regimen used in this set-up, where one patient will experience 9 episodes extra of opportunistic infections with similar course of treatment (p=*0.049)*. This implies that the TDF group has a better chance of survival and increased quality of life, as described by Sowmy V [31].

Patients with no baseline had eight times higher hazards of opportunistic infections than those who have started baseline prophylaxis with Cotrimoxazole and Isoniazid preventive therapy (p=0.009). It is clinically sound that immunologic incompetent individuals are predisposed to infection [33, 34]. Also, patients with cotrimoxazole only baseline prophylaxis were at higher probability of having OIs than their counter parts with Cotrimoxazole and Isoniazid (p=0.013). This implies that the presence of TB can change the clinical spectrum of other infections in the presence of HIV/AIDS. Stephanus K *et al.* [35] reported that, having a TB event during the follow-up was associated with a 2.71 times higher relative risk of a subsequent other opportunistic infection compared to having no prior TB during follow-up (95% CI [1.56, 4.70]). The impact of prophylaxis on the occurrence of opportunistic infections is also reported by other studies [36].

Patients with baseline BMI less than 18.5 were two times at higher risk of having opportunistic infections (p=0.016). Yoann *et al*. [37] also described low baseline BMI as a significant independent predictor for development of opportunistic infection. Another study from Nigeria has also reported opportunistic infections are most frequent in patients on ART with low body mass index [38]. For baseline CD4+ count, it was revealed that a unit increase resulted in 47% of risk reduction in OIs occurrence (p=0.039). There were also similar findings from Ethiopia [35] and Nigeria [39], which reported lower baseline CD4+ count was significantly associated with the occurrence of opportunistic infections.

Our study was not without limitation. Firstly, it was underpowered to detect the intended outcome due to inclusion of minimum number of observations for clinical outcomes. Measure of adherence by health professionals that may not fit to the reality, inability to assess the occurrence of specific OIs and selection bias due to scarcity of TDF/3TC/NVP, are some of the limitations.

CONCLUSION

In current study, there was no significant difference in mortality between those exposed to TDF *versus* AZT based regimens. The proportion of death and OIs in the subgroup belonged to TDF/3TC/EFV was lower as compared to those belonged to other regimens under study although the difference was not statistically significant. Moreover, low BMI and absence of prophylaxis at baseline were found to be an independent risk predictors for death and OIs. Higher CD4 count was found to be protective. The study highlighted the need for paying closer attention for these patients groups over the course of treatment provision.

AUTHORS' CONTRIBUTIONS

TA: conceived and led the study acquisition of data, interpretation of data, drafted the manuscript performed the statistical analysis; GM: assisted with interpretation of data, revised manuscript for intellectual content; HJ; assisted with interpretation of data, revised manuscript for intellectual content

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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