TREATMENT OUTCOMES OF TENOFOVIR AND ZIDOVUDINE BASED REGIMENS AMONG PEOPLE LIVING WITH HIV/AIDS AT JIMMA UNIVERSITY SPECIALIZED HOSPITAL, SOUTHWEST ETHIOPIA

BY: TESHALE AYELE (B.Pharm.)

A THESIS SUBMITTED TO DEPARTMENT OF PHARMACY, COLLEGE OF HEALTH SCIENCES, JIMMA UNIVERSITY: IN PARTIAL FULFILMENT FOR THE REQUIREMENTS OF MASTER OF SCIENCE (MSc.) DEGREE IN CLINICAL PHARMACY

Treatment outcomes of Tenofovir and Zidovudine-based regimens among people living with HIV/AIDS at Jimma University Specialized Hospital, Southwest Ethiopia

By:

Teshale Ayele (B.Pharm)

Advisors:

Mr. Girma Mamo. (B.Pharm, MSc)

Mr. Habtemu Jarso (BSc, MPHE)

October, 2015

Jimma, Ethiopia

Abstract

Background: Tenofovir (TDF) based regimen is one of the first line agent that is being utilized routinely since 2013 in Ethiopia. Unfortunately, there is limited information regarding the major treatment outcome measures such as: rate of CD4+ recovery, mortality and the incidence of opportunistic infections; of TDF based regimens compared with Zidovudine (AZT) based regimens.

Objective: To compare treatment outcomes of Tenofovir and Zidovudine based antiretroviral (ART) regimens among people living with HIV/AIDS at Jimma University Specialized Hospital, Southwest Ethiopia.

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 selecting records using a simple random sampling technique. Data was collected on socio-demographic, clinical characteristics of patients and drug related variables. Data was entered into EpiData version 3.1 for cleaning and analyzed using STATA 13.1. Kaplan-Meier and Cox regression was used to compare treatment outcome and identify independent predictors of treatment outcome. Hazard ratio was used as measure strength of association and p-value of <0.05 was considered to declare statistical significance. Predictors for CD4+ change were identified with mixed effect linear regression analysis. Slopes of the random effect linear regression and their 95% confidence intervals together with p-value < 0.05 was used as indicators for presence of association.

Results: Of 280 patients, 183(65.36%) were female. Of these females, 93(33.32%) belongs to Tenofovir group. The mean age of the study subjects was 32.31 $\pm$ 8.32 years. 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 opportunistic infection 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/m^2 (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/m^2 (AHR=2.06, 95% CI [1.14, 3.73]) had higher hazards of OIs.TDF group had shown potentially promising immunologic recovery (β =+34.08, 95% CI [7.8, 60.35], p=0.001) over time. And the predicted CD4+ count for TDF/3TC/EFV had (β = +347.65 cells/mm^3, p<0.001) change.

Conclusion and recommendations: TDF based combinations were promising regimens to be used in this set-up interms of suppressing opportunistic infections and immunologic recovery. However, the mortality benefit and prevalence of sub-immunologic (SO-CD4) response among the users remained uncertain.

Key-words: Treatment outcomes, Tenofovir regimen, Zidovudine regimen, Jimma University Specialized Hospital.

Acknowledgments

I would like to acknowledge Jimma University for providing me the opportunity and fund to undertake this study. My deepest gratitude will go to my advisors Mr. Girma Mamo and Mr. Habtemu Jarso.

Dr. Legesse Chelkeba, your immeasurable effort in guiding, correcting, and editing until the last stage of this work was really amazing and costly. So you deserve more than this but no words.

My dearest father, you are not the one that I can solely say thank you, but what can I say? I don't ever forget your precious, priceless, supportive and kind words that always seeds strength and hope in my daily life.
Mama,I have the utmost respect for you!

I would like to say thank you for data collectors and the entire staff members of ART clinic for their attractive co-operation and provision of necessary information during the time of data collection.

Lastly, but not least my heartfelt thanks will extend to my sweet friends and families for their immense contribution for this work.

Table of Contents

List of figures

List of tables

List of Acronyms and Abbreviation

ACTG	AIDS clinical trial group
AHR	Adjusted hazard ratio
AIDS	Acquired immunodeficiency syndrome
ART	Anti-retroviral therapy
BMI	Body mass index
CD4+	Cluster of differentiation4
CHR	Crude hazard ratio
CPT	Cotrimoxazole preventive therapy
FMoH	Federal ministry of health
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
IPT	Isoniazid preventive therapy
JUSH	Jimma University specialized hospital
NRTIs	Nucleos(t)ide reverse transcriptase inhibitors
NNRTIs	Non-nucleos(t)ide reverse transcriptase inhibitors
PEARLS	Prospective evaluation of ART in resource limited settings
PEP	Post-exposure prophylaxis
PLWHA	People living with HIV/AIDS
PMTCT	Prevention of mother to child transmission
PPMPC	Patient prescription and medication profile chart
SD	Standard deviation
SO-CD4	Sub-optimal CD4 recovery
STATA	South Texas Art Therapy Association
TB	Tuberculosis

1. INTRODUCTION

1.1Back ground

Around 1980's, Acquired immunodeficiency syndrome (AIDS) was globally emerged as a major public health threat. The reaction against it has led to unprecedented attention and commitment from the international community to improve access to Human immune virus(HIV) care, antiretroviral treatment (ART) and prevention (1,2).The introduction of potent ART has dramatically reduced HIV/AIDS associated crisis; such as, rates of mortality& morbidity, improved quality of life, revitalized communities and transformed perceptions on the disease from a plague to a manageable chronic illness (3–6).

The treatment option for HIV/AIDS has drastically changed since 1987 when the first drug, Zidovudine (AZT), was approved by the food and drug administration (FDA). The initial ART regimens used by most national treatment programs in resource-limited settings include two Nucleoside reverse transcriptase inhibitors (NRTIs) and one Non-nucleoside reverse transcriptase inhibitors (NNRTIs). The NRTIs in these regimens include AZT or Stavudine (D4T) with lamivudine (3TC); the NNRTI component has been Nevirapine (NVP) or Efavirenz (EFV). The four regimens created from these ARVs have saved hundreds of thousands of lives and provided hope to a millions (2–5,7).

Extensive use of ART may reduce the incidence of HIV infection, as the risk of transmission of the virus is lower in those receiving antiretroviral therapy than in naïve patients (8).
In between 2002–2012 , 8 million people were estimated to be receiving ART and 4.5 million deaths were averted in low- and middle-income countries (1,2,9). According to World health organization (WHO), more than 7.5 million people were receiving treatment at the end of 2012 compared to 50,000 people a decade earlier in African region .Due to increased access to ART, a total of 5.2 million deaths have been averted in low- and middle-income countries between 1996 and 2012 (9,10).

Between 1996 and 2009, 176,632 peoples were receiving ART with 52-65% ART coverage as per 2010 guideline which resulted in 160,000 life years gain among adults due to ART in Ethiopia (11). By the end of June 2013, the number of people ever started ART was 439,301 and 317,443 were receiving ART (12). A linear increase has been observed and by the end of June 2014, the number of people ever started ART was 492,649 and 344,344 people were receiving ART(13).

Currently, there are more than 20 ARV compounds approved for use in United States (US) and Europe. Multiple adult HIV treatment guidelines recommend the nucleos(t)ide reverse transcriptase inhibitors ,AZT

or TDF based regimens and most are in favour of TDF based regimens as the safer regimen for patients with no contraindication due to its proven effectiveness, favourable toxicity profile, and demonstrated regimen durability(1,14–16),except its minimal bioavailability with the current formulation i.e.,25% only (17).

TDF has a long intracellular half-life and is formulated as a single 300-mg tablet that is taken once daily. In vitro, TDF is a weak inhibitor of mitochondrial De-oxy ribonucleic acid(DNA) polymerase gamma and appears not to affect the mitochondrial DNA content in multiple cell types.(18,19).TDF has been well tolerated in clinical trials to date. In several trials, clinical and laboratory adverse events were no more common with TDF than with placebo (20). However, literatures reported that, TDF+3TC+NVP was associated with higher hazard of mortality and virologic failure when compared to AZT +3TC+NVP (21,22) and even TDF based regimens are less protective from death and OIs than AZT based regimens in HIV patients living in resource limited settings (23).

Other studies with TDF identified renal and bone toxicities as potential draw back in HIV patients (24,25). Safety issues specific to this agent such as serious renal toxicity, including acute renal failure requiring dialysis, progressive decline in renal function, proximal renal tubular dysfunction, and Fanconi-syndrome are reported by some literatures (21-24),unlike a case report from China where "a 50-year-old Chinese man with chronic hepatitis B and kidney transplantation received TDF plus entecavir ,after eight weeks, resulted in improved creatinine clearance (28)."

This may raise a question of "Is there pharmacodynamics and pharmacokinetic changes associated with TDF that may potentiate its toxicity in the presence of human immunodeficiency virus?" since toxicity reports are almost from these patient groups.

1.2. Statement of the problem

Evidences show that the current focus of resource limited settings is scaling up of access and improving the rate of retention in ART care than assuring the quality of treatment outcome(29).

In Ethiopia, in spite of the achievements in scaling up ART , losses to follow-up and early mortality remain the major gaps (30). By the end 2013 only 70.3% of individuals who ever started ART were on treatment indicating challenges in patients' retention in care (12). So the best use of ART and how patients should be maintained on successful ART regimen is the most important question to be addressed (31).

Safe and efficacious ART regimens improve patient care through rapidly restoring the immune cells, promoting adherence and alleviating the hazards of mortality(1,32).TDF is one of the ART drugs that come to be routinely utilized in the current Ethiopian practice setup since the past two years. For this drug, the recent WHO report indicated that data on the risk of major clinical events such as mortality, renal failure and, bone fractures were limited (33). But one systematic review from Cochrane library has reported that the overall mortality rate between patient taking either AZT or TDF based regimens was not significantly different(34).However; in study from India, the proportion of patients experiencing OI was greater in AZT regimen compared to TDF regimen, the difference didn't show any statistical significance (35).

Studies from developed regions showed that there were 18.0% and 18.8% immunologic failures in the EFV/FTC/TDF and EFV/3TC/AZT arms, respectively. There were no significant differences in the risk of HIV-1 disease progression or death (36).In another finding, patients receiving TDF experienced slight increase in CD4+ count from baseline compared with those receiving AZT although it is not statistically significant (37).

Even though the study done in this set-up doesn't support this fact (3),TDF based regimens has demonstrated a better outcome only when combined with Efavirenz as compared to AZT based preparations interms of its durable viral suppression and rate of immunologic recovery as reported by some studies (3,37,38). In contrary, a finding from south Africa concludes that, in population of HIV patients on treatment in resource-limited settings AZT-containing regimens appear to show a slightly protective than TDF-based regimens (23).

The decline in renal function following treatment initiation and concern related with monitoring for renal toxicity for those exposed to TDF based regimens is the potential safety issue. Many studies showed that

for those exposed to these regimens, the proportion of individuals with creatinine clearance < 50 mL/min are significantly higher than AZT based regimen exposed patients latter in the course of therapy (15,25–27,39–41).

Because of this inconclusive data currently available about the outcome of TDF based regimen compared to other regimens, we aimed to do retrospective analysis to provide a sufficient information about the major treatment outcomes; such as, mortality, rate of immunologic recovery and the incidence of opportunistic infection. In addition, there is scarcity of data specifically in JUSH on evidence presenting the comparative treatment outcome of TDF and AZT -based regimens.

Therefore, the study was aimed to fill the gap by providing a head to head comparison of the two regimens interms of immunological and clinical responses rate of the regimen among PLWHA at JUSH.

2. LITRATURE REVIEW

2.1 Literature Review

Having an evidence about the efficacy of ART agents has a lot to do with effective management of HIV/AIDS. Because of the disease's nature of incurability, People living with HIV/AIDS (PLWHA) are going to take their medication lifelong with optimum adherence in order to live longer. Therefore, selection of ARV drug will basically focuses on its: efficacy, favourable toxicity profile, and demonstrated regimen durability and minimal impact on adherence (15,17).

Different literatures discussed different treatment outcomes of antiretroviral drugs and variety of the independent predictors.

2.1.1 Clinical and immunological outcomes

The treatment outcomes of TDF and AZT based regimens are not similar due to regimens inherent differences in pharmacokinetics and pharmacodynamics nature. One prospective, randomized, multicentre non-inferiority study comparing the regimens of TDF/FTC/EFV and a fixed dose of AZT/3TC /EFV was done in Europe and USA involving 517 PLWHA who were randomly assigned to receive either regimen. At week 48, the patients treated with the TDF/FTC/EFV regimen had significantly greater increases from baseline in absolute CD4+ Cell counts (mean increase, 190 vs. 158 Cells per cubic millimetre; 95%,CI [9,55] P <0.002) and in median percentages of CD4+ Lymphocytes (CD4+ percentage) (11 % in the TDF/FTC versus10 % in the AZT/3TC group, P<0.02)(38)

A report from another a prospective study conducted in England, over 144 weeks shows patients in the TDF/FTC arm experienced an increase in CD4+ count of 312 Cells/$mm^3$from baseline compared with an increase of 271cells/mm^3 in the AZT/3TC arm, but this finding did not maintain statistical significance at 144 weeks (p = 0.09)(37).

A randomized, pragmatic, non-blinded clinical trial carried out in India, with 35 patients randomized to AZT regimen (with lamivudine and Nevirapine) and 33 patients to a TDF regimen (with Emtricitabine and Efavirenz).The proportion of patients experiencing OI was greater in AZT regimen than TDF regimen (46% vs. 31%, p= 0.22) and the death attributed to each regimen is 0 & 1 patient respectively. Patients on TDF regimen, tend to have better improvement in CD4+ values than patients on AZT regimen. The mean change

in CD4+ count from baseline was 208 ± 132cells/µl/year (mean ± SD) for AZT and 246 ±172cells/ µl/year for TDF(35).

A Comparative prospective cohort study of TDF versus AZT conducted in South Africa favoured TDF among NRTIs.In this study, the distribution of patients with over 12 months of CD4+ data for inclusion in assessing CD4+ change was 74% of TDF recipients, and 73% of AZT recipients. In the linear regression analysis, NRTI agent was significantly associated with CD4+ increase with an annual increase for TDF, and AZT of 67.0 (95% CI: 61.2, 72.8), and 53.1 (95% CI: 49.2, 56.9) cells/mm^3 (p=0.001) (41).

In a Nigerian two year retrospective, observational community based study of ART-naïve patients initiating TDF/3TC/NVP versus AZT/3TC/NVP, it was demonstrated that the annual increment of CD4+ count is much better with AZT/3TC/NVP (208 ± 166.2 Vs.221.1 ±172.6 (p=0.072(22).

In a retrospective cohort study conducted in Ethiopia, the proportion of death was slightly higher in patients exposed to AZT based regimens than their TDF counter parts (30 out of 282 versus 25 out of 258 p=0.429) (42). Another comparative retrospective cohort study from Ethiopia showed that, the ZDV/3TC/EFV had a CD4+ change of 193cells/mm^3 from base line, where as it was 173 cell/mm^3 for TDF/3TC/EFV at the 6^{th} month of therapy(3).

Table 1: Summary of treatment outcomes as reported by different literatures

Outcomes	Illustrative comparative risks		Effect	Participants	Set-up & design
	AZT/3TC/EFV/NVP	TDF/3TC/EFV/NVP			
Death	8 per 1000	4 per 1000	****RR=0.5	487	*RCT(community + hospital)[33]
	0 per 35	1 per 33	_	68	*RCT (hospital)[34]
	30 per 252	25 per 233	p=0.429	488	*Retros.cohort(hospital)[41]
OIs	16 per 35	10 per 33	p=0.22	68	**RCT (Hospital)[34]
CD4 recovery	221.1cells/mm^3/ year	208.0cells/mm^3/year	p=0.072	2174vs.813	***Observ.(Community)[21]
	208 $\pm$132cells/mm^3	246 $\pm$ 172cells/mm^3	p<0.001	68	*RCT (Hospital)[34]
	271cells/144 weeks	312 cells/144 weeks	p=0.09	229 vs.227	*RCT[36]
	158cell/48 weeks	190cells/48weeks	p<0.002	285 vs. 259	*Multicentre(prospective)[37]

*AZT/EFV VS TDF/EFV, RCT-randomized clinical trial, pros-prospective, observ.-observational

AZT/3TC/NVP VS.TDF/3TC/EFV,*AZT/3TC/NVP VS TDF/3TC/NVP****RR= risk ratio=0.5(95%CI=0.05, 5.46)

2.1.2 Predictors of treatment outcome

Experiences with ART suggest that adherence is arguably the most important factor in affecting treatment outcomes. The study done in South Africa found that, patients on twice AZT/3TC/NVP or daily doses TDF/3TC/EFV reported better adherence (>80%) than patients on multiple doses per day and were more likely to take their medications when away from home(43).

A retrospective, comparative cohort study of AZT versus TDF based regimens in Zambia showed different independent factors to affect the treatment outcomes: in both regimens Low BMI, low CD4+ count, low haemoglobin, and advanced disease stage at baseline were all associated with elevated hazard of mortality. Women had higher risk of death, while individuals on tuberculosis treatment at time of ART initiation had lower risk of death (14).

An HIV outpatient study: a Prospective, multicentre, observational cohort study, showed that amount of CD4+ cell counts at time of ART initiation and overall ART use duration were significantly associated with cause of death(44).

A retrospective cohort study conducted in multiple countries has linked sex as the most important independent predictor for immunologic outcome. Even though it is not a head to head comparison, this study shown that females have a better CD4+ count change when on AZT based regimens while males have better CD4+ improvement when on TDF based regimen at the end of 6^{th} month of therapy(38).

A prospective Evaluation of Antiretroviral in Resource Limited Settings, (PEARLS) study of the AIDS Clinical Trials Group (ACTG) has shown a significant interaction between sex and treatment outcomes. Women randomized to EFV/FTC/TDF had lower risk of a safety endpoint compared to women randomized to EFV+3TC/ZDV (HR 0.50, CI 0.39–0.64)(36).

Many studies done across different parts of the world has reported the impact of ART initiation at different CD4+ count will resulted in differences in treatment outcomes. Accordingly, people started ART between CD4+ 200-350 were 68% less likely to die, 63% less likely to need hospitalisation, and 39% less likely to drop out of care, compared to people who began treatment at CD4+ 200 or lower(18,45,46).

A retrospective comparative study was done in Nigeria with intention of comparing ART associated adverse drug reactions as one independent variable to affect treatment outcome. According to this study compared to patients on TDF, ADR was less likely to occur in patients on AZT with AOR =0.18 (95% CI: 0.05-0.64) versus AOR =0.24(95% CI: 0.7-0.9) respectively(47).

In the Prospective Evaluation of Antiretroviral in Resource Limited Settings (PEARLS) study, there were 95 (18.0%) and 98 (18.8%) immunologic failures in the EFV/FTC/TDF and EFV+3TC-AZT arms, respectively, and the range of the relative risk difference was 0.72 to 1.27.Treatment failure relative risk did not change significantly over time ($p = 0.89$ (36).

2.2 Conceptual frame work

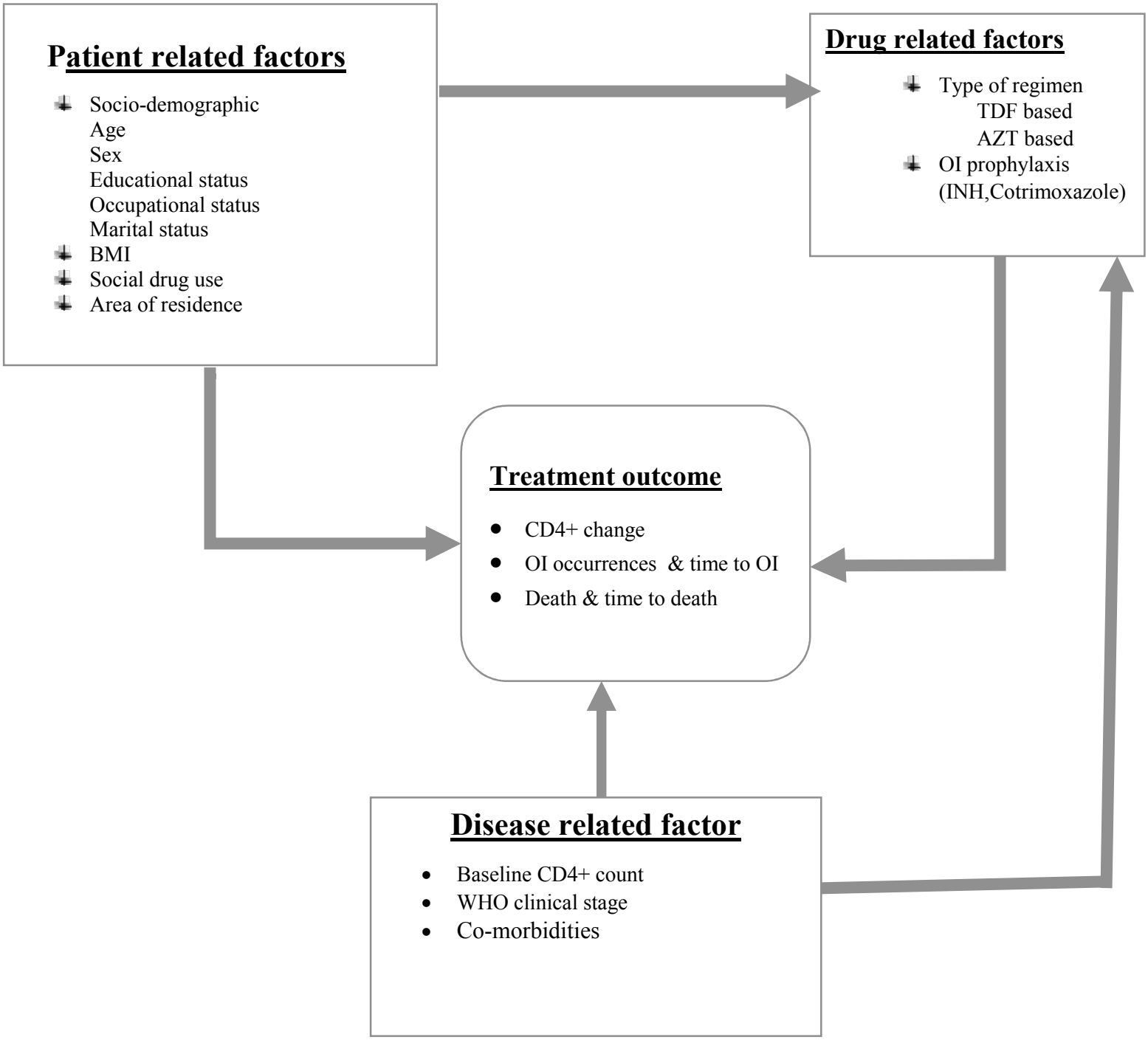


Figure 1: Conceptual frame work for factors associated with treatment out comers

2.3 Significance of the study

Despite the progress in improving access of antiretroviral treatment, important questions remain on the best use of ART and how patients should be maintained on successful regimen (31).

The treatment outcomes related to ART in developing countries like Ethiopia, may differ from that in developed countries because of the high prevalence of conditions such as low literacy, tuberculosis, Anaemia, malnutrition, and frequent initial presentation with advanced HIV disease and inadequate outcome monitoring (48).

Lack of well controlled studies in Ethiopia hinders both clinicians and policy makers to identify population specific safe agents and enforces them only to rely on data derived from other population. The findings generated by this study can be an input for clinicians, policy makers, reconsideration of the current already developed ART guidelines, quality control and procurement agencies. It also serves as an input for further research.

3. OBJECTIVES

3.1General objective

To compare treatment outcomes of TDF and AZT based regimens among people living with HIV/AIDS at Jimma University Specialized Hospital, South west Ethiopia, from September 3, 2012 to July 31, 2014

3.2 Specific objectives

- To assess clinical outcomes of TDF and AZT based regimens among people living with HIV/AIDS
- To assess immunologic outcomes of TDF and AZT based regimens among people living with HIV/AIDS.
- To identify predictors of treatment out comes of TDF and AZT based regimens among people living with HIV/AIDS.

4. METHODS AND PARTICIPANTS

4.1 Study area and period

The study was conducted at Jimma University specialized Hospital, which is located in Jimma town; Jimma Zone, Oromiya Region, Southwest Ethiopia and is about 346km away from the country's political centre, Addis Ababa.

Jimma University Specialized Hospital (JUSH) is one of the oldest public hospitals found in the south - western part of the country that runs under Jimma University. It is currently the only teaching and referral hospital in this part of the country serving a total population of about 15 million. The hospital has ART clinic with about 7486 clients. The ART clinic services involve HIV care and treatment, TB treatment, post exposure prophylaxis service and prevention of mother to child transmission services (49). The study was conducted from February 10 /2015 to March 10/2015.

4.2 Study design

A hospital based retrospective cohort study design was used

4.3 Source population

All HIV infected adult patients who were on ART (TDF and AZT based regimens) with regular follow up at JUSH ART clinic.

4.4 Study population

All adult patients who were on TDF and ZDV based regimens between September3, 2012 and July 31, 2014 who fulfilled the eligibility criteria

4.5 Inclusion and exclusion criteria

- **Inclusion criteria**
  - Patients who were on AZT and TDF based first line regimens
  - Who have at least six months of follow-up
  - Those who have CD4+ count at least at base line and six month
  - Patients older than 14 years old.
  - Those with good adherence
- **Exclusion criteria**
  - Pregnant women

4.6 Sample size determination and sampling technique

- **Sample size determination**

Sample size determination was guided by the number of patients on TDF/3TC/NVP, whereby only 70 patients fulfil the inclusion criteria and all were included in the study. A frequency matching was used with each category of 70 subjects to control the confounding effects of non-nucleoside reverse transcriptase inhibitors (NNRTIs). So patients from the other regimens were selected based on the above figure to make the unexposed to expose ratio 1:1.Therefore a total of 280, with 140 exposed and 140 unexposed charts of patients were reviewed.

Sampling technique

From those ART initiated patients at the start of the study period and treated for first six months, only the charts of AZT and TDF based regimens users were selected and served as sampling frame from which the exposed and the unexposed groups were selected by simple random sampling technique.

❖ Selection of exposed

Exposed groups (n1 = 140) were those initiated with TDF based regimen which were identified from patient charts of hospital records. All patients exposed to TDF/3TC/NVP were include and a simple random sampling technique was used to select representative sample from TDF/3TC/EFV exposed patients by using computer generated random number.

❖ Selection of unexposed

One unexposed patient was selected per exposed and making the total unexposed patients 140 (n2 = 140). Unexposed groups were those patients initiated on AZT based regimen and selected by similar manner as exposed.

N.B: Participants in the cohort are qualified as exposure group if they were initially commenced on TDF based regimens and unexposed group if they started AZT based regimens initially (21).

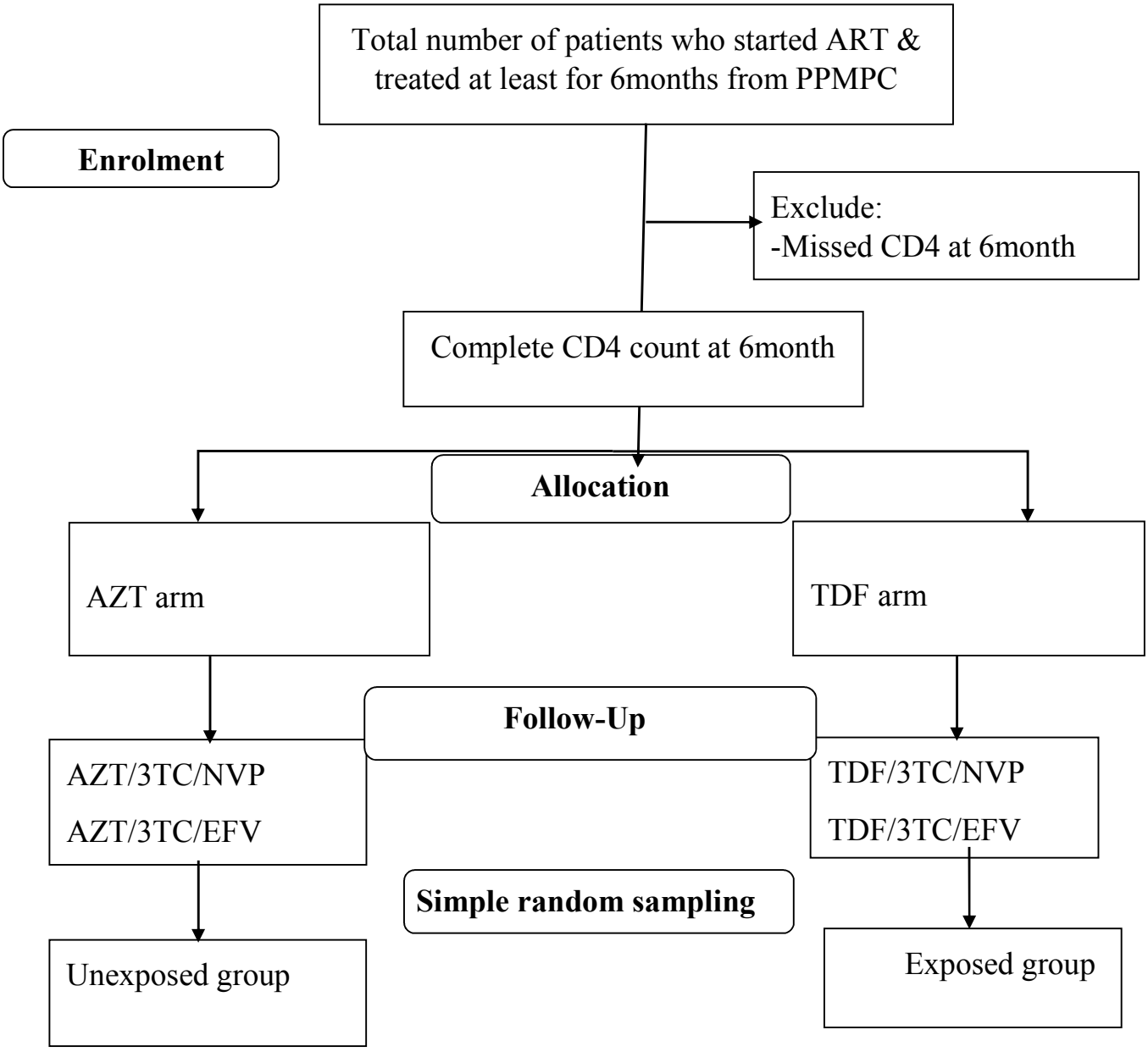


Figure 2: Summary of sampling procedure

Adopted from: *http://www.consort-statement.org*

4.7 Study variables

- **Dependent variables**

Primary outcome: Treatment outcomes (CD4+ change, occurrence of Death and OIs)

Secondary outcome: time to treatment outcome

- **Independent variables**
  - ❖ **Patient Related**
    - ✓ **Socio-demographic**
      - o Age, Sex
      - o Marital status
      - o Educational Status
      - o Occupational status
    - ✓ Area of residence
    - ✓ Habit of social drug use
    - ✓ BMI
  - ❖ **Drug Related Factors**
  - ✓ **Types of regimen**
    - ☞ AZT based regimen
    - ☞ TDF based regimen
  - ✓ **OI prophylaxis**
    - ☞ INH
    - ☞ Cotrimoxazole
  - ❖ **Diseases Related Factors**
  - ✓ Baseline CD4+ count
  - ✓ WHO clinical Stage
  - ✓ Co-morbidities

4.8 Data collection Instrument & Procedure

The data collection procedure was a multi-stage process. The first stage was reviewing the number of patients and their card numbers who started therapy with the specified time period. Then, the card number of each patient was cross-checked with the current ART regimen on the patient medication prescription profile card that found in the ART pharmacy. Finally those who met the inclusion criteria were stratified and sampling was made. 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 (1,3,50,51).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.

4.9 Data Quality Assurance

Data collection tool was carefully prepared to enable the data collectors to collect all necessary information needed to address study objectives. A one day training on data collection tool and general procedures of data collection was given for two pharmacists (B.Pharm) and two ART nurses who were assigned as data collectors and one Medical intern who was act as supervisor. Pre-test was conducted on 5% of the eligible records. The supervisor had supervised data collectors and facilitated the daily activities. All filled checklist was reviewed for completeness and consistency on daily basis by principal investigator.

4.10 Data processing and analysis

Data was entered into Epi-Data 3.1 and exported to STATA 13.1(STATA Corporation, Texas, USA) for cleaning and analysis. Descriptive analysis was performed and results was presented by text, tables and charts. χ^2 test was used to check the adequacy of cells for binary logistic regression. The survival experience of the patients was checked by Kaplan-Meier (log-rank test).Multicollinearity test was performed to check for collinearity between independent variables. For death and occurrence of OIs, 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 $\leq$ 0.11 in bivariate regression were considered as candidates for multivariable regression. Multivariable Cox regression was performed to identify independent predictors of treatment outcome.

Hazard ratio was used as measure strength of association and p-value < 0.05 was considered to declare a statistical significance. Propensity score matching was used to elucidate the morbidity effect of each ART regimen relative to the base regimen (AZT/3TC/NVP).

Mixed-effect linear regression analysis was performed to identify predictors CD4+ change. This modelling approach was used because mixed models take into account both the within and between sources of variation, are flexible enough to account for the natural heterogeneity in the population, and can handle any degree of missing and drop-outs in the data (52). Bivariate regression was performed to identify candidate variables for multivariable regression. Variables with p-value ≤ 0.25 in bivariate regression was considered as candidates for multivariable regression. Multicollinearity between independent variables was checked and multivariable linear regression was performed to identify independent predictors of CD4+ change. The slopes of the random effect linear regression & their 95% confidence intervals together with p-value < 0.05 was used as indicators for the presence of association. Marginal analysis was conducted to predict the two year mean change in CD4+ count attributed to each regimen.

4.11 Ethical consideration

The present study was approved by the Institutional Review Board of JUSH, Jimma, Ethiopia and the need for informed consent was waived because of the retrospective, anonymous nature of the study.During data collection, confidentiality was ensured and for this reason, name and address of the patient was not recorded in the data collection check list.

4.12 Dissemination plan

The final result of the study will be disseminated to responsible bodies such as Pharmacy department of Jimma University, JUSH administrators, Ethiopian Federal Ministry of Health, Ethiopian Food, medicines and health care Administration and Control Authority. Finally, the study finding will be submitted to reputable and peer-reviewed professional journal for publication.

4.13 Operational definition and definition of terms

Good adherence: estimated adherence level of >95%, (51) as recorded by ART physicians/Nurses. **Adult:** Age above 14 years(50).***CD4+ count change***: A number of CD4+ counts >50cells/mm^3 gain from baseline after starting therapy (measured at least at 6th month) (55).**Sub-optimal CD4-response:** net CD4+ gain <50cells/µl measured at six month(56). **Co-morbidity:** any medical condition concomitantly occurring with HIV/AIDS(57) and its occurrence is not due to the opportunity created by HIV/AIDS. Example, Diabetes mellitus. **OI prophylaxis**: a medication the patient is taking in order to prevent opportunistic infections. (E.g. INH and Cotrimoxazole)(58). **Treatment outcome:** refers to death, change in CD4+ number, and occurrence of at least one of the opportunistic infections. **Incident OIs**: The onset of new infection after three months of ART initiation in a patient initially free of any clinically evident infection (59). **Social drugs use**:Refers to patients behaviour of using at least one of these social drugs i.e. alcohol, khat or cigarette (60). **Censored**: If for a given patient, the study ends while the patient is still without event of interest (i.e. the event defining failure does not occur) (61). **Event:** is the life time of the concerned unit(e.g. death)(61).**Died:** a patient who dies of any reason after six months of ART**. Regular follow-up:** those who come to ART clinic according to their appointment date. **Lost to follow-up:** Refers to a patient who has missed clinical or drug pick-up appointment permanently(51).

5. RESULTS

5.1. Characteristics of the study groups

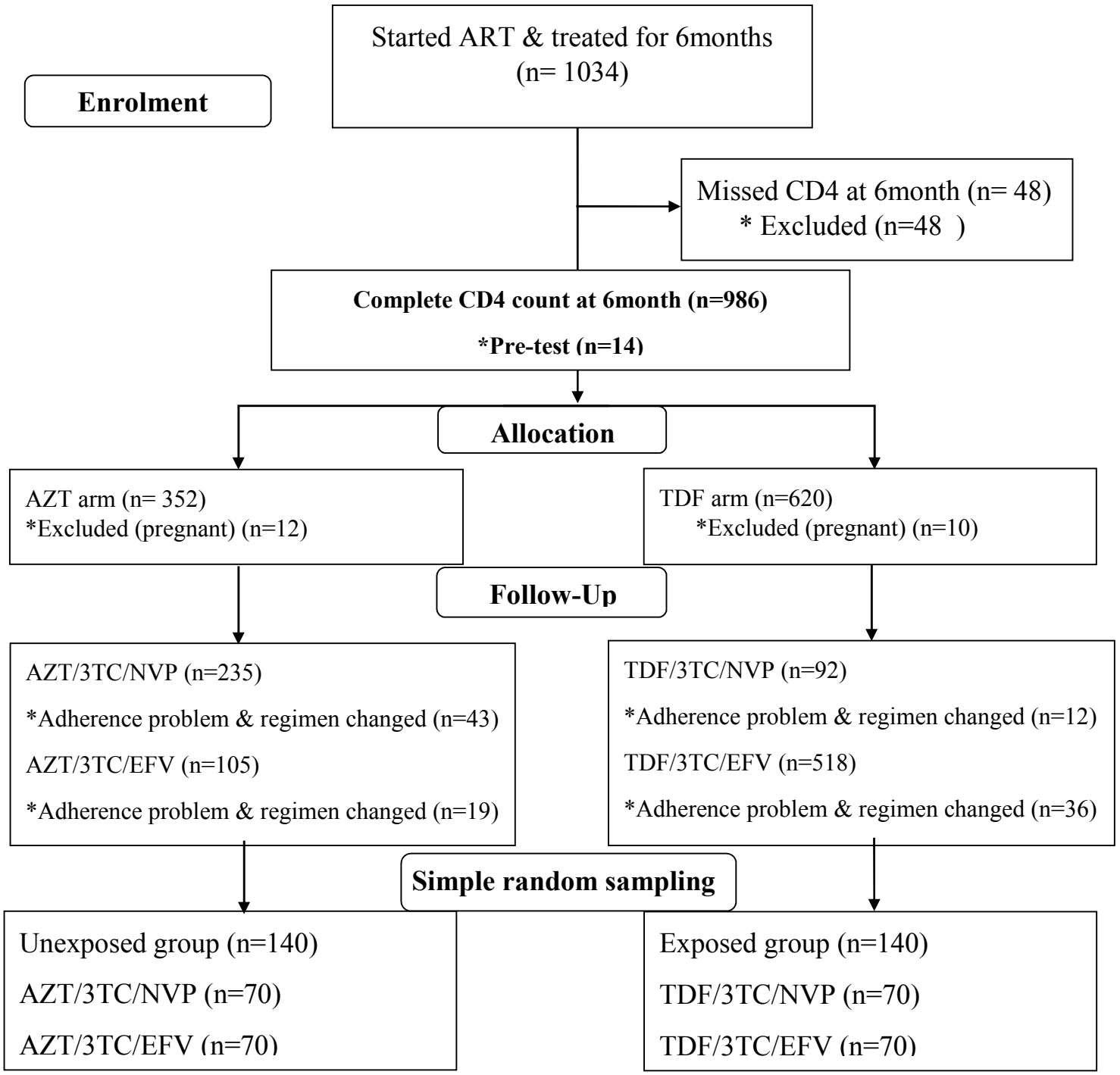


Figure 3: Sample recruitment chart at JUSH, from February10 to March1, 2015

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 exclude 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. Since only 70 patients were remain on TDF/3TC/NVP that governed the sample selection. With simple random sampling technique, 280 patients were selected.

Therefore, a cohort of 280 patients on TDF and AZT based regimens was followed retrospectively for 24 months. The study was conducted by dividing the total sample in two major classes as TDF as an exposure group and AZT as unexposed, and AZT based regimen was chosen as a base regimen for the comparison. Subjects were considered as censored if: lost on follow-up or lived beyond the study period.

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 exposed and unexposed groups respectively. The mean $\pm$ standard deviation (SD) duration of follow up was 714.2 $\pm$ 69.6 and 708.8 $\pm$ 78.9 days (*p=0.753*) among exposed and un-exposed respectively. Study participants retained in the cohort for different length of follow up time: they stayed for a minimum of 7.4 and 8.9 months for exposed and unexposed groups respectively (*p=0.743*).

At the end of follow-up period, 128 (91.43%) versus 131(93.6%)) completed their follow up, Six (4.3%) versus five (3.6%) deaths and 6(4.3%) versus 4 (2.9%) lost for follow-up were recorded from unexposed and exposed groups respectively (*p=0.769*).

5.1.1. Description of socio-demographic variables

The mean $\pm$ SD age of the study participants was 32.3 $\pm$ 7.4 and 32.3 $\pm$ 9.2 years for the exposed and unexposed groups respectively. Similarly, the mean $\pm$ SD baseline body mass index (BMI) was 19.7 $\pm$ 3.4 and 20.4 $\pm$ 3.0kg/m^2 respectively. Relatively, patients from TDF group had low BMI (<18.5kg/m^2) and low mean CD4+ count (<200cells/mm^3) at baseline as compared to AZT group (20.4$\pm$ 3 versus 19.7$\pm$3.44) and (175.2 $\pm$ 89.14 versus 164.6 $\pm$ 83.4, respectively.

Majority of the study subjects 183 (65.36%) were females and they were relatively equally distributed among exposed and unexposed groups, 90 (64.3%) versus 93(66.4%). Nearly half, 139(49.64%) were orthodox by religion. Of them more than half, 80(57.1%) were from unexposed group. Those who were

Muslims by religion contributed almost comparative for both groups, i.e. 45(32.1%) and 42(30%) for exposed and unexposed groups respectively.

More than half, 153(54.64%) of the study subjects were married. Of these, 77(55%) were from exposed group. The lowest share of marital status was contributed by those who were widowed and they were 8(5.7%) and 13(9.2%) from exposed and unexposed groups respectively.

Twenty six (9.3%) were smokers and they were equally distributed among the groups. Sixty five (23.21%) of them were alcohol consumers and their proportion was relatively higher in unexposed group than exposed, 38(27.1%) versus 27(19.3%). One hundred and twenty two (43.57%) of the study subject had post primary level of education and they comprised 70(50%) of the exposed group. Twenty two (15.8%) of the exposed group were illiterate. This category contributed for 30(21.4%) of unexposed groups. One hundred and six (37.9%) patients had primary level of education and majority of them 58(41.4%) were from unexposed group. Of the two hundred and seven (73.93%) urban residents, 110(78.5%) belongs to unexposed group.

One hundred and twenty-six (45%) of study subjects were employees of different government institution and self-running business owners. Of these, 68(48.6%) were from exposed group.

Table 2: Comparative baseline socio-demographic characteristics of the study cohort at JUSH, from February 10 to March 10, 2015

All n=280	**Exposed group**	**Unexposed group**
Variables	**(n=140)**	**(n=140)**
Sex Male	50(35.7)	47(33.6)
Female	90(64.3)	93(66.4)
Age **<25**	27(19.3)	32(25.9)
26-45	108(77.1)	98(85.9)
>45	5(3.6)	10(7.2)
BMI <18.5	52(37.1)	37(26.4)
≥18.5	88(62.9)	93(73.6)
Educational level		
Illiterate	22(15.8)	30(21.4)
Primary	48(34.2)	58(41.4)
Post-primary	70(50)	52(37.2)
Residence Urban	97(69.3)	110(78.5)
Rural	43(30.7)	30(21.5)
Occupation		
Employed	68(48.6)	58(41.5)
Unemployed	46(22.8)	55(39.2)
Housewife	26(18.6)	27(19.3)
Religion		
Orthodox	59(42.1)	80(57.1)
Muslim	45(32.1)	42(30)
Others	36(25.8)	18(12.9)
Marital status		
Married	76(54.3)	77(55.0)
Single	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)
Yes	27(19.3)	38(27.1)

*BMI-body mass index, OIs-opportunistic infections

5.1.2 Baseline clinical characteristics

Overall, females contribute 90 (64.3%) and 93(65.4%) for the exposed and unexposed groups respectively. At baseline, more subjects from exposed group were at WHO clinical stage III, 47(33.6%) whereas proportional quantity, 47(33.6%) of subjects from unexposed group were at WHO clinical stage II. Very few of them, from exposed and unexposed groups, 15(10.5%) versus 14(10.0%) started treatment at WHO stage IV. Of the study subjects, 110(78.6%) in exposed and 79(56.4%) in unexposed group were functionally classified as "working, W" and those who were bed ridden comprised only 6(4.3%) and 5(3.6%) respectively. There were 20(15.3%) and 17(12.1%) of patients diagnosed with TB and initiated anti TB drugs from exposed and unexposed groups respectively at the start of the study. Patients with initial diagnosis of co-morbidity other than TB were only 6(2.1%), of these 4(2.9%) of them belongs to exposed group.

Cotrimoxazole preventive therapy (CPT) was the most frequently used prophylaxis at baseline. There were 86 (61.4%) and 99(70.7%) patients on CPT from exposed and unexposed groups respectively. In contrary, 17 (12.2%) from exposed and 11(7.8%) from unexposed group had no baseline prophylaxis.

Table 3: Comparative baseline clinical characteristics of the study cohort at JUSH, from February 10 to

Variables	Exposed n (%)	Unexposed n (%)
Baseline CD4+ count		
(Mean ± SD)	164.64 ± 83.36	175.21 ± 89.14
<200	92(65.7)	74(53.9)
≥200	48(34.3)	66(47.1)
WHO stage		
I	32(22.9)	36(25.7)
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)
A	24(17.1)	56(40.0)
B	6(4.3)	5(3.6)
TB (treatment)		
No	120(84.7)	113(87.9)
Yes	20(15.3)	17(12.1)
Prophylaxis		
CPT+ INH	37(26.4)	30(21.5)
CPT alone	86(61.4)	99(70.7)
Neither	17(12.2)	11(7.8)

March 10, 2015

CPT-Cotrimoxazole, INH-Isoniazid, CD4+-cluster of differentiation4, SD-standard deviation

5.1.3. Baseline CD4+ count

More than half (59.3%) of the study subjects had a baseline CD4+ count ≤200cells/mm^3 and majority of them, 92(65.7%) were from exposed group. However, when they are described interms their mean ± standard deviation (SD), it was 164.64 ± 83.36 and 175.21 ± 89.14 for exposed and unexposed groups respectively. Stratified analysis over the starting regimen showed that, the mean CD4+ count lied between,139.7±71.6 cells/mm^3,which belongs to AZT/3TC/NVP for males and 197.4 ± 97.43 cell/mm^3 that was to AZT/3TC/EFV for females as described in figure 3 below. Except for males commenced on TDF/3TC/NVP (178.5±61.76 cells/mm^3), females had higher baseline mean CD4+ count.

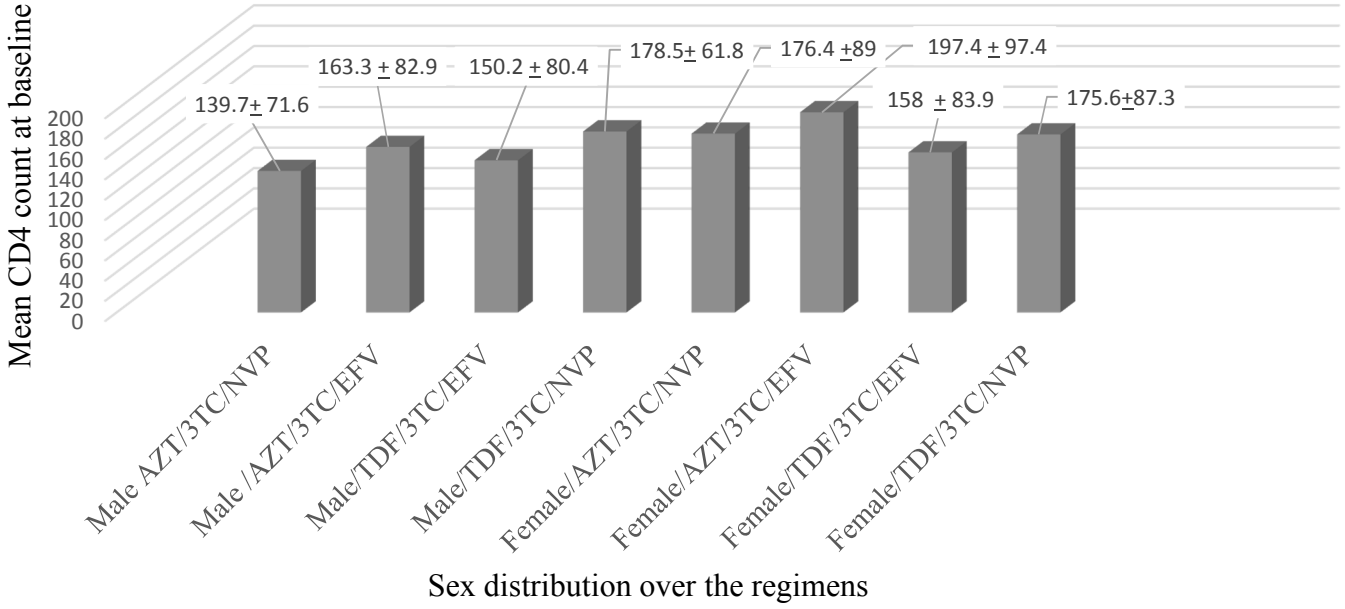


Figure 4: Baseline CD4 counts distribution (Mean + SD) of the cohorts at JUSH, from February10 to March10, 2015

5.2. Treatment outcomes

5.2.1 Clinical outcome

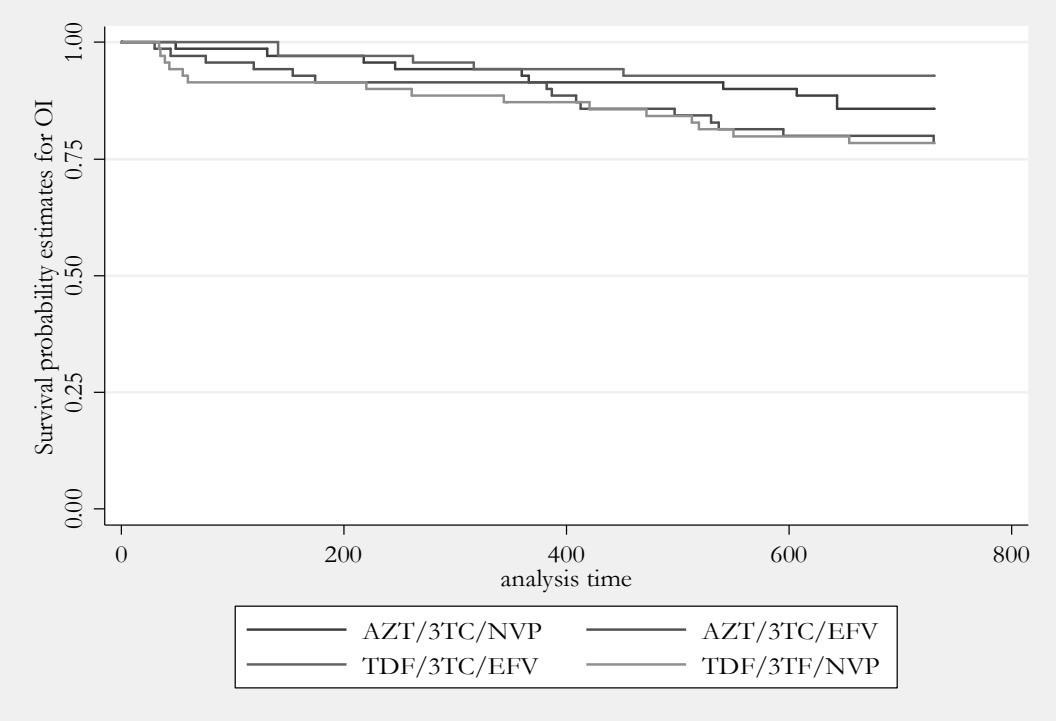
5.2.1.1 Death

The total proportion of death among exposed and unexposed group was 3.68% and 4.48% (*p=0.759*) 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%); however, the

observed proportion was similar i.e. 3(4.44%), for the rest of the regimens. The survival time, mean ± SD of exposed and unexposed groups does not show any statistically significant difference; 713.46 ± 4.411 and 709.57 ± 4.983 days respectively (*p= 0.743*).

5.2.1.2 Occurrence of opportunistic infections

The proportion of opportunistic infection was 14.3 %and 17.9 % respectively among exposed and unexposed groups (p=0.47). The mean ± SD survival time to opportunistic infection 656.574 ± 14.58 and 654.793 ± 14.339 days respectively among the groups (p=0.462). For each separate regimen, the mean survival time showed patients exposed to TDF/3TC/EFV had favourable survival experience; and the difference was marginally significant as shown by the Kaplan-Meier survival estimate (fig 5).



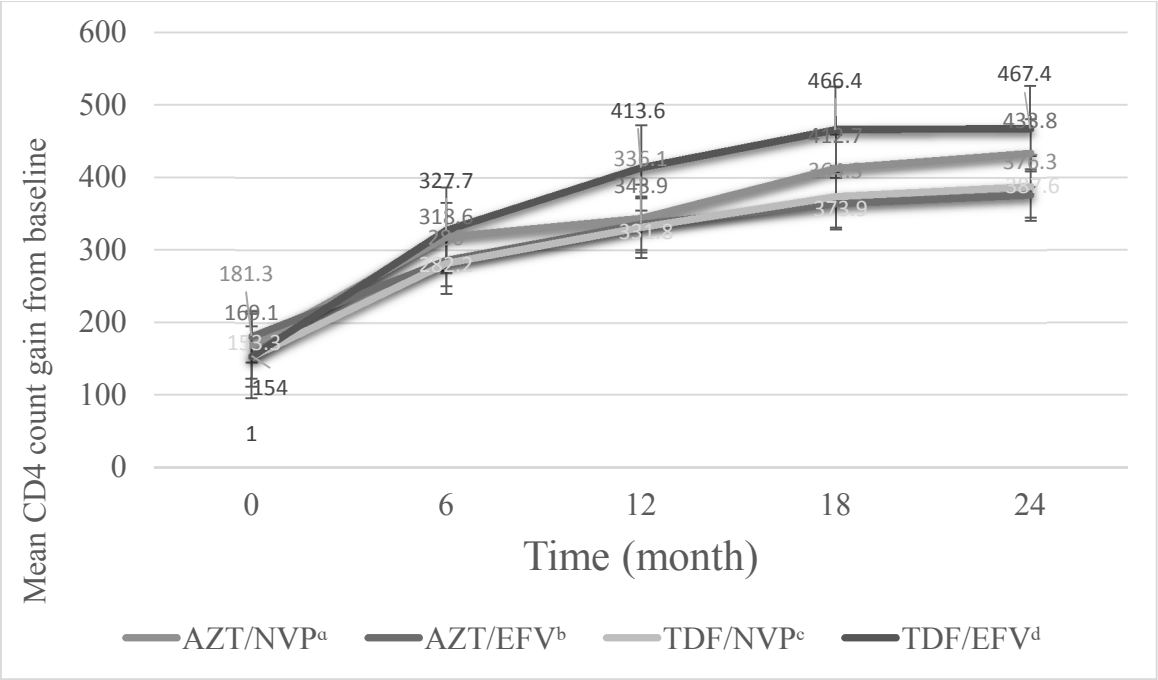
Log-rank p=0.063

Figure 5: Survival estimates for opportunistic infections among the cohort at JUSH, from February 10 to March 2015

5.2.2 Immunologic outcome

The mean change in CD4+ over the last two years of the study subjects was depicted in the figure 6 below. The overall mean CD4+ showed promising outcome among the exposed than unexposed group, (321.7±164.8 versus 299.4 ±126.1 cells/mm^3).

If each regimen's contribution is considered, by assuming baseline mean CD4+ count measured at zero time, the maximum mean CD4+ count gain at any given time was attained by TDF/3TC/EFV and the minimum belong to AZT/3TC/EFV.



*Missing values per each regimen at 12, 18 and 24 months respectively: ^{a}(2, 7, 11) ^{b}(11,3 ,2) ^{c}(7 , 1 ,9) ^{d}(5 ,12 ,4)

Figure 6: The mean gain in CD4+ count of patients treated by AZT and TDF based regimens at JUSH, from February 10 to March 2015

At 6month the prevalence of sub-optimal CD4+ response (net CD4+ gain <50cells/μl) was assessed and it was 67(23.95%).Of this figure, 20(30%) belongs to TDF/EFV, 19(28.3%) to AZT/EFV and 16(23.8%) to TDF/NVP. Earlier at the initiation of ART, the CD4+ count showed a linear trend but it becomes more flat after 18th month with a very minimal gain irrespective of the regimen.

Table 4: Summary of the major comparative treatment outcomes for TDF and AZT based regimens at JUSH, from February 10 to March 10, 2015

Outcomes	Illustrative comparative effects		*p-value*	Number of participants
	AZT/3TC/NVP/EFV	**TDF/3TC/EFV/NVP**		
*Death	6 per 140	5 per 140	*0.758*	280
Time to death (mean ± SD)	709.57 ± 4.983	713.46 ± 4.411	*0.743*	-
*OIs	25 per 140	20 per 140	0.416	280
Time to OIs (mean ± SD)	654.793 ± 14.339	656.574 ± 14.58	*0.462*	-
**Immunologic recovery	319.11 & 281.54	347.65& 295.73	*p<0.001*	280

AZT VS TDF combinations

- Time to death: AZT group (95%CI=699.799, 719.332, days), TDF group (95% CI=704.811, 722.103)
- Time to OIs: AZT group (95%CI=626.688, 682.897, days), TDF group (95% CI=627.998, 685.151)

**Marginal effects: AZT/3TC/NVP & AZT/3TC/EFV, TDF/3TC/EFV & TDF/3TC/NVP

5.3 Predictors of treatment outcomes

5.3.1 Death

Smoking, presence of comorbidity other than TB and functional status are removed from the analysis because of their exponential distribution. The survival experience among the groups was compared by log-rank test. Bivariate cox-regression was conducted with socio-demographic and base line characteristics such as baseline CD4+ count, WHO clinical stage, functional status, presence of TB at baseline, history of prophylaxis use, ART regimen.

On bivariate cox-regression, absence of TB at baseline found to increase the risk of death; although it was statistically insignificant (AHR=1.49, 95%CI [=0.19, 11.67], *p=0.702)*.

Baseline CD4+ count,sex and BMI were identified predictors for death on bivariate cox-regression (p<0.11).Hence further regression was conducted by including ART regimen as it was a variable of interest. The adjusted multivariate cox-regression showed BMI being the only independent predictor for death.

Therefore, 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*).

Baseline CD4+ count was also another independent predictor of death. Threfore,a unit increment in baseline CD4+ count was found to be protective (AHR=0.82,95%CI [0.809,0.998],p=0.019).

As seen from the analysis, patients initially commenced 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*). However, the difference among the groups didn't show any statistical significance.

Even though statistically insignificant, females were likely to be at higher risk of death (AHR=6.14, 95% CI [0.78, 48.34], *p=0.084*) as compared to males in the cohort.

Table 5: Crude and adjusted cox-proportional hazard regression for predictors of death of the cohort at JUSH,from February 10 to March 10,2015

Variables		CHR [95%CI]	p-value	AHR [95%CI]	p-value
Sex	Male	1		**1**	
	Female	5.6 [0.71,43.5]	0.10	**6.14[0.78,48.34]**	**0.084**
Age	≤25	2.4[0.69,8.65]	0.167		
	26-45	1			
	>45	2.3[0.27,18.6]	0.455		
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			
	Post-primary	1.73[0.43,6.93]	0.44		
Residence	Urban	1			
	Rural	1.66[0.49,5.69]	0.42		
Religion	Orthodox	1			
	Muslims	0.66[0.17,2.55]	0.55		
	Others	0.35[0.04,2.87]	0.33		
Occupation	Employed	1			
	Unemployed	0.87[0.25,3.09]	0.83		
	Housewife	0.39[0.05,3.21]	0.38		
Marital status					
	Married	1			
	Single	1.98[0.48,8.27]	0.35		
	Widowed	0.56[0.07, 4.79]	0.60		
	Divorced	2.89[0.56, 14.92]	0.204		
Alcohol	No	1			
	Yes	1.18[0.31,4.46]	0.803		
Baseline CD4+ count		**0.89[0.981,0.998]**	**0.017**	**0.82[0.809,0.998]**	**0.019**
WHO staging	I	1			
	II	1.79[0.35,9.2]	0.488		
	III	0.74[0.10,5.2]	0.76		
	IV	2.43[0.34,17.23]	0.375		
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					
	CPT + INH	1	1		
	CPT	1.27[0.26,6.11]	0.75		
	Neither	2.5[0.35,17.77]	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

5.3.2. Predictors of opportunistic infection

Similarly log-rank test was done to compare survival experience among the groups and bivariate cox-regression analysis was conducted for clinical and socio-demographic variables, excluding smoking, functional status and presence of comorbidity other than TB .Considering all the assumptions and for the model fitness, a cox-proportional hazard regression was conducted to identify independent predictors for development of opportunistic infections. Therefore, from all the factors mentioned above, history of baseline prophylaxis, baseline CD4+ count and BMI of the patient were found to have statistical association with occurrences of OIs.

As compared to those who had initiated both Cotrimoxazole and isoniazid preventive therapy at base line patients with no prophylaxis were found to be under higher risk of developing opportunistic infection (AHR=8.22,95% CI [1.7,39.77],*p=0.009*).Similarly, those patients who started prophylaxis with Cotrimoxazole only have had at increased risk to have opportunistic infection in their future life time regardless of the ART regimen (AHR=6.15,95% CI [1.47,25.67],p=*0.013*),however they were in a better position relative to those that have no any prophylaxis at base line.

Low BMI (BMI<18.5kg/m^2) was another opportunistic infection risk predictor among the patients. Therefore, those with low BMI were almost two times at higher risk of developing opportunistic infections (AHR=2.05, 95% CI [1.13, 3.73], *p=0.018*).

Baseline CD4+ count was also another significant predictor, that conferred significant protection against the occurrence of OIs (AHR=0.53, 95% [0.42, 0.998**],** p=0.039).

In addition, patients in unexposed, i.e. (AZT) group, had 23% higher hazard of OIs than their exposed (TDF) counterparts (AHR=0.77, 95% CI [0.43, 1.40], *p=0.405*), even though it was statistically insignificant.

Living in rural area was associated with higher hazards of OIs, whereas drinking alcohol has conferred protection against OIs attack ((AHR=1.44, 95% CI [0.21, 1.09], *p=0.08*) and (AHR=0.48, 95% CI [0.2, 1.14], *p=0.095*)) respectively, but both are statistically insignificant.

Table 6: 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			
	Female	1.32[0.69,2.52]	0.398		
Age	<25	1.26[0.634,2.494]	0.502		
	25-45	1			
	>45	0.85[0.64,2.51]	0.827		
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		**1**	
	Rural	1.97[0.88,4.12]	0.098	**1.4[0.21,1.09]**	**0.08**
Occupation	Employed		1		
	Unemployed	1.28[0.69,2.39]	0.421		
	Housewife	0.57[0.21,1.51]	0.259		
Marital status	Married	1			
	Single	1.67[0.804,3.50]	0.168		
	Divorced	1.54[0.719,3.28]	0.268		
	Widowed	1.52[0.52,4.44]	0.447		
Religion	Orthodox	1			
	Muslims	0.86[0.7,2.68]	0.51		
	Others	0.49[0.14,3.87],	0.44		
Alcohol	No	1			
	Yes	0.49[0.21,1.15],	0.101	**0.48[0.20,1.14]**	**0.095**
Baseline CD4+ count		0.56[0.36,1.003]	0.058	**0.53[0.42,0.998]**	**0.039**
WHO clinical stag	I	1			
	II	1.13[0.51,2.52]	0.758		
	III	1.16[0.52,2.58]	0.720		
	IV	1.24[0.42,3.62],	0.697		
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	**1**		**1**	
	CPT alone	**7.12[1.71,29.57]**	**0.006**	**6.15[1.47,25.67],**	**0.013**
	Neither	**9.23[1.92,44.44]**	**0.003**	**8.22[1.7,39.77],**	**0.009**

Results of propensity score matching analysis

With consideration of adherence and frequency of NNRTIs as a matching variables, occurrence of OI as an outcome variable and ART regimen as treatment dependent variable after adjusting for all other potential confounders other than smoking, functional status, and other comorbidity, the propensity score matching analysis output revealed that:

*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 (table7).

Table 7: 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 exposed and unexposed groups except variables that doesn't meet the criteria of propensity score matching analysis.so it is assumed that the exposed and unexposed 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.**

5.3.3 Predictors of CD4+ change

Considering consecutive CD4+ count measurement was as an outcome variable, multilevel mixed effect linear regression was conducted. The slope of random-effect multiple linear regression was used to interpret the overtime change in CD4+ count attributed to the predictor variables.

Therefore, the average gain in CD4+ count achieved at every visit among the cohort was 38cells/mm^3 (β=38.18 95% CI [33.11,43.24],p<0.001) with the conditional correlation coefficient of 64.9%, i.e. 64.9% of the variability in CD4+ count response of a subject between two visits was explained by unobserved patient specific factors.

Among the groups, 38.99% of the variation in CD4+ change was explained by differences in the regimens where as 25.34% of the variation is attributed to other regression variables (p<0.001), showing an important heterogeneity between patients groups.

In the overall analysis, keeping other factors constant, older age is found to be one of the negative predictors of CD4+ count change. So younger patients (age<25 years) were found to have +66 gain in CD4+ count every six months as compared to those with ages ≥45 years (β=-66.19 [-126.68,-5.70**]**,p=0.032).

Among the predictor variables, female sex was strongly associated with progressive CD4+ count gain at each visit. So females had+39 CD4+ cells advantage over time (β =33.86, 95% CI [33.11, 43.24], p=0.013) as compared to their male counterparts.

Those patients with high body mass index (BMI≥18.5kg/m^2) had a significantly higher CD4+ change (+32 cell/mm^3) over time than those who had BMI<18.5kg/m^2 (β=-32 [-60.16, -4.27], p=0.011).

Baseline CD4+ count was also another independent predictor for CD4+ advantage over time (β=0.879, 95% CI [0.70, 1.06], p<0.001*).*

More importantly, patients randomized TDF group had a significant CD4+ count gain per visit compared with their AZT counterparts (β =34.08, 95% CI [7.80, 60.35], p=0.027).

According to this work, other baseline patient factors such as WHO clinical stage**,** baseline TB, educational status, area of residence, religion, occupational status, marital status, alcoholic behaviours, and history of prophylactic use had no significant association forCD4+ change.

Table 8: Random-effect linear regression analysis of trend of CD4+ count (slope, cells/mm3/6 month) at JUSH, from February 10 to March 10, 2015

		Unadjusted		Adjusted	
Variable		β [95% CI]	p-value	β [95% CI]	p-value
Sex	Male	**0**		**0**	
	Female	**52.373[21.22,84.24]**	**0.001**	**33.86 [33.11,43.24]**	**0.013**
Age	<25	**0**		**0**	
	25-45	**-53.15[-90.03,-16.27]**	**0.005**	**-27.32[-59.3,4.66]**	**0.094**
	>45	**-120.87[-191.24,-50.49]**	**0.001**	**-66.19[-126.68,-5.70]**	**0.032**
BMI	<18.5	**-48.08[-80.42,- 15.74]**	**0.004**	**-32.77[-60.16,-4.27]**	**0.011**
	≥18.5	**0**		**0**	
Educ. level					
	Illiterate	-0.5[-42.86,41.86]	0.982		
	Primary	14.42[-19.59,48.44]	0.406		
	Post-primary	0			
Residence					
	Urban	0			
	Rural	-12.35[-47.18,22.54]	0.488		
Occupation					
	Employed	0		0	
	Unemployed	-1.40[-32.23,32.44]	0.936	3.96[-26.04,33.95]	0.796
	House wife	51.50[10.2,92.80]	0.015	21.35[-18.42,61.12]	0.293
Marital status					
	Single	30.25[-11.18,71.68]	0.152	40.45[0.52,80.37]	0.069
	Married	0		0	
	Divorced	13.06[-27.17,53.29]	0.525	6.42[-32.27,45.11]	0.745
	widowed	-19.89[-79.56,39.77]	0.513	-2.33[-55.27,50.6]	0.931
Religion					
	Orthodox	0		0	
	Muslim	22.91[-12.00,57.83]	0.198	20.83[-8.86,50.53]	0.166
	Other	0.21[-40.70,41.13]	0.992	-12.09[-46.89,22.71]	0.496
Alcohol	yes	-26.1[-62.15,9.94]	0.156	8.48[-22.88,39.83]	0.596
	No	0		0	
ART regimen					
	TDF group	11.58[-18.98,42.15]	0.458	34.08[7.80,60.35]	0.027
	AZT group	0		0	
Baseline CD4+ count		**0.97[0.80,1.15]**	**0.000**	**0.879[0.70,1.06]**	**0.000**
WHO stage	I	0			
	II	-16.76[-57.59,24.06]	0.421		
	III	-23.17[-64.32,17.97]	0.270		
	IV	-29.27[-86.35,27.81]	0.315		
TB (treatment)	No	0		0	
	Yes	-48.18[-85.37,5.00]	0.081	-20.74[-59.05,17.57]	0.289
Prophylaxis	CPT + INH	0		0	
	CPT alone	-29.40[-65.65,6.85]	0.112	-10.34[-40.57,19.88]	0.502
	Neither	-40.89[-97.93,16.16]	0.160	-22.3[-70.33,25.73]	0.363

β-the slope of regression line, CPT-Cotrimoxazole preventive therapy, TB-tuberculosis, INH-Isoniazid, TDF-Tenofovir, AZT-Zidovudine

5.3.4 Results of marginal analysis

To predict the expected change in CD4+ count among exposed and unexposed groups at the end of treatment period, post-estimation marginal analysis was conducted using STATA 13.1 and the regression output showed that:

*In ***exposed*** groups, the predicted mean CD4+ count for patients treated with TDF/3TC/EFV had 347.65 cells/mm^3 of CD4+ change, and it was 295.73cells/mm^3 of CD4+ for those treated with TDF/3TC/NVP.

*Similarly, in ***unexposed*** groups, the predicted mean CD4+ count for patients treated with AZT/3TC/NVP had 319.11 change, whereas the change was 281.54cells/mm^3 for those treated with AZT/3TC/EFV. This figure was exactly the expected increase in CD4+ count associated with each regimen and has a crucial clinical implication in guiding clinicians to initiate on which regimen as the role of good immunologic recovery in treatment HIV infection is multidimensional. So this section of analysis (table 9) clearly showed that the overall outcome was better in exposed groups than in unexposed.

Table 9: The predicted mean CD4+ change of patients treated with AZT and TDF based regimens at JUSH, from February 10 to March 10, 2015,

Status	Status	Delta-method				
		Margins	Standard error	t	[95% CI]	*p-value*
Unexposed	AZT3TC/NVP	**319.11**	19.34	16.50	281.02,357.20	***p<0.001***
	AZT/3TC/EFV	**281.54**	**18.39**	**15.31**	245.31,317.77	***p<0.001***
Exposed	TDF/3TC/NVP	**295.73**	18.39	16.08	259.50,331.96	***p<0.001***
	TDF/3TC/EFV	**347.65**	**18.39**	18.90	311.42,383.89	***p<0.001***

*Adjusted for all predictor variables among the exposed and unexposed groups except variables that doesn't meet the criteria of marginal analysis. So it is assumed that the exposed and unexposed groups have the uniform distribution in confounder variables included in the model for mean CD4+ change in the multiple linear regression analysis.

6. DISCCUSSION

This study summarized the clinical and immunological impact of TDF and AZT based regimens in one of resource limited settings of Ethiopia. The key questions addressed in this study, were: the prevalence of death and opportunistic infections among the cohort, the relative morbidity benefit of the regimens, and the immunologic response attributed to each regimen as well as the factors associated with; clinical and immunological responses of the study subjects.

6.1 clinical outcome

6.1.1 Death; occurrence and predictors

In this population with good adherence (adherence ≥95%)(51), the proportion of death among TDF group (exposed) and AZT groups (unexposed) groups is 3.57% and 4.29% (*p=0.759*) respectively. The survival time, mean ± SD, of exposed and unexposed groups does not show any statistically significant difference and it was; 713.46 ± 4.411 and 709.57 ± 4.983 days respectively (*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 .

The current finding is in line with the study by Damtew et al.(42), which conducted in Somali region, karamara hospital with similar design. According to this study, the proportion of death among patients exposed to TDF and AZT based regimens was 29.8% and 31.9 %(*p=0.429*) respectively. The higher proportions of death might be due to larger sample size (485 vs. 280 subjects) relative to the latter study. Another possible justification could be, the current study includes only patients with good adherence, whereas patients in earlier study are included irrespective of their adherence status. The exclusion of patients with follow-up less than six months may also contribute for the lowest proportion of death recorded in current study as most of the deaths occur within four months post initiation of ART(62). Involvement of adherence supporters, reduced in stigma related to HIV, improvement in the prophylactic and VCT services, might have played a role in reducing the incidence of death in current study.

In the current study, the risk of death in patients with BMI<18.5Kg/m was more than two times higher (AHR=2.21, 95%CI [1.93, 11.97], p=0.049) compared to those with a BMI ≥ 18.5 kg/m^2. Study conducted

in Malawi showed individuals with BMI<16 kg/m2 had six times higher risk of dying in the first three months than those with a normal nutritional status (63). Study from *Asgaire et al*. (64) estimated one year mortality was nearly 50% among patients with severe malnutrition in Tanzania. This implies that the nutritional supplement program for those who are candidates for food by prescription has to be enhanced since BMI is an indicator of patient nutritional status that may be influenced by late-stage AIDS conditions, such as wasting syndrome and opportunistic infections, or progression of the HIV itself. Another study conducted in Somali region showed individuals who have BMI<18.5kg/m^2 at baseline had more than two times higher comparative risk of dying (42)..

In our finding, as baseline CD4+ count increased by a unit, the risk of death was decreased by18% (AHR=0.82, 95% CI [0.809, 0.998], p=0.019). Study from USA(58) 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 (65) and Ethiopia (42). Our finding disagreed with study from Nigeria (66).The reason might be due to exclusion of patients with baseline CD4+ count less than 50cell/mm^3 in the former study.

Patients exposed to AZT based regimen had 33% higher hazard of death than their TDF exposed counter parts (AHR=0.67, 95%CI [0.20, 2.40], p=0.52). The result was statistically insignificant possibly due to inclusion of very few clinical events in the analysis. 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](41).The finding is largely inconsistent with another study by *Babafemi.A* (23) which showed that AZT based regiments are more protective than TDF based regimen. The reason for the deviation might be due to shorter duration of the former study and the inclusion of patients with good adherence as well as the inclusion of patients with only have more than six months of follow up as most deaths were occurred early in the first four months since the start of therapy as reported by other findings from Ethiopia (62).

6.1.2 Opportunistic infections, occurrence and predictors

This study also determined the prevalence and associated predictors of opportunistic infections (OIs) in a group of patients receiving TDF and AZT based regimens in resource limited setting in Ethiopia. The overall prevalence of opportunistic infections in TDF (exposed) and AZT (un-exposed) group is 14.3 % (95% CI=0.094, 0.212) and 17.9 %(95%CI=0.123, 0.252). The mean $\pm$ SD survival time to opportunistic infection 656.574 $\pm$ 14.58 and 654.793 $\pm$ 14.339 days respectively (p=0.462). The propensity score matching analysis finding, which treats individual regimen with respect to the base regimen (AZT/3TC/NVP) was absolutely in favour of TDF/3TC/EFV. The independent predictors for the occurrence of OIs for this specific cohort as identified by multivariate cox-regression were history of baseline prophylaxis, baseline CD4+count and low base line body mass index(<18.5kg/m^2).However, it lacked statistical significance, patients randomized to AZT based regimen were 23% at higher risk of developing OIs.

This finding is concurrent with the randomized open label clinical trial done in India which revealed that proportion of opportunistic infection is slightly higher in patients randomized to AZT group than TDF, however the figure is quite higher than the current findings (46% vs. 31%, *p=0.22*)(35).The difference in figure could be due to the difference in study design, set-up,sampe size(70 vs. 280) and the exclusion of subjects with follow-up of less than six month in recent study which may underestimate the prevalence.Possibly,the improvement in quality of care, improved access to preventive therapy, and involvement of adherence supporters might reduce the prevalence of opportunistic infections in this set-up

In addition to its 23% OIs risk reduction (AHR=0.77 95%CI [0.43, 1.4], p=0.405), the slightly higher median survival time in TDF group may also explain the survival advantage of this regimen. A prospective open cohort study by Samuel et al (54) conducted in Urban slums of Kenya indicated that patients commenced on TDF based have relatively higher mean survival than its AZT counterpart (*61 vs.56.5 months*) respectively.

Form the matching estimator analysis, it was found that the individual morbidity benefit of TDF/3TC/EFV was incomparable with the rest of the regimen when each regimen were compared with the base regimen. Based on this finding, there was one opportunistic infection prevented every 14 patients treated using this regimen (*p=0.026*). Relative to the base regimen, AZT/3TC/EFV was the least protective regimen ever used in this set-up. Accordingly, one patient will experience 9 episodes of opportunistic infections over the

two years course of treatment (*p=0.049)*.This implies that the exposed group have a better chance of survival and increased quality of life. As described by Sowmy V. (35) the overall quality of life due OI is higher in TDF group.

The other dimension of this study was identifying the predictors of opportunistic infections in the cohort. According to the finding, patients with no prior exposure to prophylaxis before initiation of AZT or TDF based combination regimens have almost eight times at higher hazards of developing opportunistic infections than those who have baseline prophylaxis with Cotrimoxazole and Isoniazid preventive therapy(AHR=8.22, 95% CI[1.7, 39.77],p=0.009). It is clinically sound that immunologic incompetent individuals are predisposed to infection(57,58). So this might lead to the conclusion that HIV patients must be put on prophylactic preventive therapy irrespective of the ART regimen they are commenced on if they have no any contraindications (42), but 28 (10%) of the patients have no baseline prophylaxis without documented contraindications (reason) in this study.

Even though the hazard is relatively lower for those who are only initiated with Cotrimoxazole preventive therapy, these patients are still at higher probability of having OI attack than their counter parts with dual preventive therapy (AHR=6.15, 95% CI [1.47, 25.67],p=0.013). This implies the presence of TB can change the clinical spectrum of other infections in the presence of HIV/AIDS. Stephanus K *et al* (67) has reported that, in South African, 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 clinical implication of this finding is that Co-trimoxazole prophylaxis should be initiated after HIV diagnosis and continued during ART as this is associated with additional gains in life expectancy(68) and effort should have to be made for initiation of Isoniazid preventive therapy (IPT) in a candidate patients apart from difficulty of excluding active TB in patients with moderate or advanced immunodeficiency.

The impact of prophylaxis on the occurrence of opportunistic infections is also reported by other studies (58). But in study done in North-western Ethiopia, there was no any statistical association between occurrence of OI and use of prophylactic therapy(69). The deviation might be due to insignificant number, 45(10.6%) out of 423, of patients were on prophylaxis in the former study.

Low BMI was another risk predictor for the development of opportunistic infections among patients treated with TDF and AZT based regimens. So those with baseline BMI less than 18.5 were two times at higher risk of having opportunistic infections (AHR=2.05, 95% CI [1.14, 3.73],p=0.016) irrespective of the ART

regimen commenced.Yoann.*et al*. (70) also described low baseline BMI as a significant independent predictor for development of opportunistic infection in patients receiving ART. Another study from Nigeria has also reported opportunistic infections are most frequent in patients on ART with low body mass index(71).This implies that the nutritional status of patients need to be assessed frequently and supplementation with adequate nutrition together with ART is beneficial.

The role of higher baseline CD4+ count was also revealed in our finding. As it increased by a unit, the risk of OIs occurrence was reduced by 47% (AHR=0.53, 95% [0.42, 0.998**],** p=0.039).There were also similar findings from Ethiopia (69) and Nigeria(72), which reported lower baseline CD4+ count was significantly associated with the occurrence of opportunistic infections.

6.2 Immunologic outcome

The current study has also included immunologic findings among patients exposed to TDF and AZT based regimens. Analysis of mean CD4+ gain every six month showed that, the maximum gain in mean CD4+ count was attained by TDF/3TC/EFV followed by AZT/3TC/NVP and TDF/3TC/EFV at any given time in the course of therapy. AZT/3TC/EFV had the least immunologic recovery over the entire treatment course. The CD4+ count shows a linear trend but it becomes more flat after 18^{th} month with a very minimal gain irrespective of the regimen. The overall prevalence of sub-optimal CD4+ response was found to be 67(23.95%). More interestingly, majority of sub-optimal immunologic responders were belongs to TDF/3TC/EFV (30%) whereas the lowest proportion of sub-optimal immunologic responder were observed from AZT/3TC/EFV (17.9%) at the first six month.

Our finding of mean CD4+ recovery was in agreement with a randomized multi-centre open-label study from Gallant et al.(16), where a maximum immunologic response was achieved by TDF/3TC/EFV followed by AZT/3TC/EFV (270 vs. 237cells/mm^3) at 96 weeks. Another finding from Nigeria indicated that TDF/3TC/NVP is much more inferior to AZT/3TC/NVP interms of immunologic recovery (208 vs.221.1 cells/mm^3) at 12months of therapy(22). The difference in the outcome of TDF/3TC regimen when combined with EFV and NVP may be due to negative pharmacokinetic or pharmacodynamics interaction between this NRTI backbone and NVP.

However, the current results are largely inconsistent with the cross-sectional study conducted in JUSH which revealed that the maximum possible immunologic recovery is attained with AZT/3TC/EFV

(193cell/$mm^{3)}$ and TDF/3TC/EFV be the one with a mean CD4+ gain of 173 cells/mm^3 (3). The reason could be the smallest sample size considered in the previous study (21 vs.140 subjects).

The finding from the marginal analysis may further explain the power of TDF/3TC/EFV over the other regimens. From the output of marginal analysis, the change in mean CD4+ count is significantly higher in TDF based EFV regimen. Therefore, the difference in the predicted CD4+ count change of the regimens has clinical, immunological and economic implications as well. It may also serves as a scientific guide for clinicians in such a way that which regimen should has to be commenced depending up on the patients clinical indication.

The bi-phasic CD4+ count response shown in our finding was also reported by other findings (55,73) as a rapid increase of memory CD4+ cells (a high CD4+ count slope) in the first several months after treatment initiation succeeded by a slow increase in naive CD4+ cells (smaller slope compared to the initial several months).The linear trend in CD4+ increment at early phase of of therapy became flat with minimal CD4+ gain latter after 18^{th} month of treatment irrespective of the regimen used.So "when will target CD4+ count (500-800cells/mm^3) be attained after initiation of ART?" is the question to be addressed by further study.

Immunologic response after six months of ART indicates a favourable clinical outcome in HIV-1 infected patients regardless of virologic response(74).Several studies has reported that as many as 8 - 40% of patients on ART do not show a significant increase in CD4+ cell count despite viral suppression (55,56,75).Our finding in general is almost consistent with these studies.

Till this days, studies are unable to justify the impact of ART regimen on sub-optimal immunologic recovery. So, it is not surprising that most the patients in this study are from TDF base regimens. As the recovery of the CD4+ T cell count is hindered by several patient and viral factors, including: residual viral replication, impaired thymic function, advanced age, enhanced T cell activation and apoptosis, genetic variations, baseline anaemia and poor adherence (55,56,76), our finding might not quest the efficacy of TDF based regimens in resource limited settings, even though it needs a further workup with adequately powered and high methodological quality study design.

Study by Mauro et al (77) has confirmed that older age as a key independent predictor for sub-optimal immunologic response as thymus activity decreases with age (78). In our study the mean age of this population group was higher than those with concordant response. So our finding agreed with the previous

results. And also older age is statistically significant negative predictor of CD4+ gain up on multiple regression.

The pre-treatment CD4+ count in relation to sub-optimal immunologic response: however, is controversial as some literatures favour higher baseline CD4+ (>200 cells/mm^3) (69) & explains it as "starting treatment at higher CD4+ cell counts limits the scope for further increases". Other literatures favoured lower baseline CD4+ count (<200cells/mm^3) and this is biologically plausible given that a low nadir pre-treatment CD4+ cell count is thought to be suggestive of more extensive depletion of CD4+ cells in the gut-associated lymphoid tissue during acute HIV infection, and may be delayed or refractory to reconstitution with ART (80).

In summary this study has short comings including absence of viral marker measurement to conclude the rate of sub-optimal immunologic recovery among the patients. So further study needed to be conducted and the possible reason why most of them are confined to TDF based regimen has to be justified. Because, lack of knowledge about this subgroup may contribute to inadequate clinical management, as current HIV treatment guidelines do not provide specific applicable guidance (55).

6.2.1 Predictors of CD4+ change

The overall random effect linear regression analysis had pointed out that, baseline BMI, sex, age, baseline CD4+ count, and exposure to TDF based regimen were independent predictors for CD4+ change over time. The marginal effects of each regimens confirmed that the immunologic outcome associated with TDF based EFV preparations was more convincing and made it the golden regimen to be utilized in this setup (margins=347.65cells/mm3/ , *p<0.001*) followed by AZT/3TC/NVP (m=319.11cells/mm^3, *p<0.001)*and TDF/3TC/NVP(m=295.73,p<0.001) respectively. However, AZT/3TC/EFV had lowest predicted change in CD4+ count (m=281.54, p<0.001). This implies that this regimen has minimal immunologic response and its clinical utilization need to be reconsidered.

Females had a greater CD4+ improvement over time. Accordingly, every visit of female patients was associated with the average CD4+ count of 39 cells/mm^3 (β =33.86 [33.11, 43.24], p=0.013).Similar study from Lao democratic republic strengthen this finding (50). But it was inconsistent from the study in Asia (73) probably due to differences in study setup and sample size (1676 versus 280) ,where females contribute only 26% of the sample analysed.

The impact of age on immunologic recovery was well described(78) and this study had found concordance with previous findings. Accordingly, the CD4+ gain attained by younger (<25years) patients was +66 cells/mm^3 as compared to those older than 45 years of age (β=-66.19, 95% CI [-126.68,-5.70], p=0.032). The finding is consistent with the studies from Ghana (52) and Asia (73) which reported the inverse relationship between age and CD4+ gain. This is mainly due to failure of cellular expansion or non-sustained cell survival in the periphery or age related central degeneration of thymus function as patients become aged (55).

In the cohort, those with high BMI, (BMI ≥18.5 kg/m^2) , had a better immunologic outcome and each visit was associated with 32 cells/mm^3 of CD4+ count advantage as compared with patients with low BMI, (BMI<18.5 kg/m^2) (β=-32.22, 95% CI [17.23,51.85],p<0.001).This is concurrent with the study by Bastard *et al.*(50), in which higher BMI (>18kg/m^2) was reported to have a protective effect for CD4 count increment at 9month of therapy (HR= 0.39, 95% CI 0.25-0.60).This implies that higher BMI is a sign of good nutritional status and it is fertile ground for better immunologic revival.

The baseline CD4+ count was another positive predictor for successful immunologic revival. So a patient has a 0.879 CD4+ cell count advantage over time , for every count higher in initial CD4+ count, when

compared to his/her counterpart (β=0.879 95% CI [0.70,1.06],*p<0.001)*.This finding is consistent form study by Mustapha *et al* (52) and Lawrence et al. (79) in which higher baseline CD4+ count was associated with good immunologic outcome. This might be due to less extensively depleted immune system will be boosted easily after initiation of ART. The overall clinical and immunological findings were suggestive of better outcome of ART if initiated at higher CD4+ count. This finding also agrees with the recent WHO ART guidelines (81) which described the initiation of ART irrespective of WHO stage and CD4+ count in adolescents and adults.

Incontrary,the finding disagrees with some studies showing poor immunologic recovery including discordant responders when ART was commenced at higher CD4+ count(82).This may be due to the goal CD4+ in HIV patients (500cells/mm^3) (83) can be attained immediately in those with higher base line CD4+ and further increment could be impossible. The reason for the deviation might be due to differences in sample size and set-up. The multicenterity of the previous study might contribute for the difference.

From this study, patients randomized TDF group had a significant CD4+ count advantage per visit relative to their AZT randomized patients (β =+34.08, 95% CI [7.80, 60.35], p=0.001).This study is consistent with most of the previous findings that described TDF based regimens as the one with better immunologic outcome (16,34,38,84).

Strength and limitation of the study

One of the strength of our study is the application of principle of propensity score matching and post estimation marginal analysis, a concept similar to randomized clinical trial to reduce the impact of baseline confounders on clinical and immunologic outcome. In addition to this the design: cohort study; which is appropriate for risk estimation among exposed and unexposed groups and it also eliminates recall bias. Restriction of adherence and frequency matching is also another strength of this study.

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. Another major hiccup of this study is measure of adherence by health professionals that may not fit to the reality. It also doesn't assess the occurrence of specific OIs and the impact of comorbidities other than TB on the treatment outcomes. Selection bias due to scarcity of TDF/3TC/NVP, absence of viral load measurements, removal of creatinine clearance and haemoglobin from the analysis as well as wide confidence intervals due to inclusion of few events are some of the other limitations.

7. Conclusion and recommendation

7.1 Conclusion

The results of this study suggests that TDF based regimens especially, TDF/3TC/EFV had improved clinical and immunologic outcome. But findings derived from its impact on death and opportunistic infections should be interpreted cautiously since the observed events are clinically comparable. The immunologic recovery associated with each regimen was clearly showed TDF based regimen was promising. Interms of immunologic recovery, AZT based NVP regimen to be the next from TDF/3TC/EFV which takes an upper hand in every outcome assed.

The survival benefit of TDF based regimen; especially TDF/3TC/EFV, was better relative to AZT based regimen. The regimen AZT/3TC/EFV was associated with relative poor outcome and its clinical utilization should be discouraged. TDF/3TC/NVP use and its procurement should also be reconsidered.

Females and patients with low body mass index deserve more attention as they carried the higher hazards of mortality. In addition patients with low body mass index and those with no or prophylaxis only with Cotrimoxazole should be treated watchfully as they were at risk of having OIs. Since aged patients, those with baseline line CD4+ count<200 cells/mm^3 and patients with pre-treatment BMI<18.5 were poor immunologic responders, they need special attention while delivering care and treatment

7.2 Recommendations

To improve care and treatment outcome in PLWHA, multi-sectorial involvement is required. So the following recommendations are forwarded from findings of this research.

❖ For pharmaceuticals Fund and Supply Agency

- The procurement of TDF based NVP combinations and AZT based EFV combinations has to be revised

❖ For JUSH, head office

- The role of adherence supporters has to be intensified so as the fate of patients who were lost on follow-up can be traced.
- Providing necessary materials for CD4+ measurement every six month should be strengthened.

❖ For JUSH ART clinic

- Recording of complete patient assessment should be given a due attention.
- Patients should have complete assessment and laboratory work-up as recommended by the guideline for CD4+, Haemoglobin level and renal function since these tests are major indicators of safety and efficacy associated with the current regimens.
- Patients should be monitored for adherence with care.
- The habit of prophylaxis provision with both CPT and IPT simultaneously should be revised since more protection was conffered by this practice.

❖ For researchers

- Further research has to be conducted on the mortality impact of TDF with better study design and sufficient sample size.
- The impact of NVP on the TDF/3TC combination has to be justified by further research.
- The overall status of SO-CD4+ in this set-up needs to be researched urgently with adequate sample size and high quality methodological study design.

8. References

1. Tirfe ZM, Ahmed TA, Tedla NB, Debere MK, Alamdo AG. Immunological responses of HIV / AIDS patients treated with Nevirapine versus Efavirenz based highly active anti-retroviral therapy in Addis Ababa , Ethiopia : A retrospective cohort study. 2013;1508:1502–8.

2. Solomon SS, Ganesh AK, Mehta SH, Yepthomi T, Balaji K, Anand S, et al. Immunologic response among HIV-infected patients enrolled in a graduated cost-recovery programme of antiretroviral therapy delivery in Chennai , India. Indian J Med Res. 2013;6(137):1145–53.

3. Alemayehu llelisa duga, Gizat Molla Kassie BAH. Comparative study of the effects of antiretroviral therapy(ART) on the CD4 cell count in the jimma university specialized hospital. J Pharm scintfic Innov. 2014;3(4):310–4.

4. Tang MW, Kanki PJ, Shafer RW. A Review of the Virological Efficacy of the 4 World Health Organization – Recommended Tenofovir-Containing Regimens for Initial HIV Therapy. J CID. 2012;54(15).

5. Ruan Y, Xing H, Wang X, Tang H, Wang Z, Liu H, et al. Virologic outcomes of first-line HAART and associated factors among Chinese patients with HIV in three sentinel antiretroviral treatment sites. Trop Med Int Heal. 2010;15(11):4–10.

6. Albrecht D, Altfeld M, Behrens G, Bredeek UF, Buhk T, Dickinson L, et al. HIV Medicine [Internet]. 2007. Available from: www.HIVMedicine.com

7. Cole SR, Thomas JC, Porter K, Jay S, Davidian M. Timing of HAART Initiation and Clinical Outcomes in Human Immunodeficiency Virus Type 1 Seroconverters. Arch Intern Med. 2011;171:1560–9.

8. Franco CB. Triple-combination rilpivirine, emtricitabine, and tenofovir (Complera/Eviplera) in the treatment of HIV infection. Dove Press JournalPatient Prefer Adherence. 2013;7:531–42.

9. World health organization. Global update on HIV tretment : 2013. 45 p.

10. Kuti MA, Adesina OA, Awolude OA, Ogunbosi BO, Fayemiwo SA, Akinyemi JO, et al. Dyslipidemia in ART-Naive HIV-Infected Persons in Nigeria—Implications for Care. J Int Care Assoc Provid AIDS. 2014;1–5.

11. UNAIDS. UNAIDS Report on the global AIDS epidemic,. 2012.

12. Ethiopia FD republic of. Country progresive report on HIV/AIDS. 2014;25.

13. Health FDR of EM of. Health sector development programme IV:Annual performance report. 2014.

14. Spaulding A, Gw R, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naïve individuals. cochraine database Rev. 2010;(10).

15. Chi BH, Mwango A, Giganti M, Mulenga LB, Tambatamba-chapula B, Reid SE, et al. Early clinical and programmatic outcomes with tenofovir-based antiretroviral therapy in Zambia. J Acquir Immune Defic Syndr 2010. 54(1):63–70.

16. Pozniak AL, Gallant JE, Dejesus E, Arribas JR, Gazzard B, Campo RE, et al. Tenofovir Disoproxil Fumarate, Emtricitabine, and Efavirenz Versus Fixed-Dose Zidovudine/Lattmivudine and Efavirenzt in Antiretroviral-Naive Patients Virologic, Immunologic, and Morphologic Changes—A 96-Week Analysis. J Acquir Immune Defic Syndr. 2006;43(5):535–40.

17. Clayden BP, Collins S, Frick M, Harrington M, Horn T, Jefferys R, et al. HIV.HCV.TB 2015 pipeline report. 2015. 30 p.

18. World health organization. Antiretroviral therapy for HIV infection in dults and adolescents recommendations for a public health approach. 2010.

19. Gallant JE, Pozniak AL, Miller MD, Coakley DF, Lu B. Efficacy and Safety of Tenofovir DF vs Stavudine in Combination Therapy in Antiretroviral-Naive Patients:A 3-Year Randomized Trial. Jounal Am Med Assoc. 2004;21287:191–201.

20. Gallant JE, Deresinski S. Tenofovir Disoproxil Fumarate: at Johns Hopkins University School of Medicine. JClinical Infect Dis. 2003;37(1):944–50.

21. Moyo C, Schuttner L, Mulenga LB. Comparative outcomes of tenofovir- and zidovudine-based antiretroviral therapy regimens in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2012;58(5):475–81.

22. Scarsi, K.Darin, K.Rawizza H, Meloni, SEisen, G.Chang, C. Olaitan, R. Agbaji, O.Gashau, W. Murphy, R.Kanki P. TDF-3TC-NVP is inferior to AZT-3TC-NVP in a large ART program in Nigeria. J Acquir Immune Defic Syndr. 2010;517–21.

23. BABAFEMI AA. Comparison of clinical and immunological responses to Zidovudine(AZT) and Tenofovir(TDF) containing ARV regimens in patients taking HAART at Roma health service area of Lesetho. J Acquir Immune Defic Syndr. 2010;45(7):8–11.

24. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults : the first 4 years. AIDS 2007. 2007;21(10):1273–81.

25. Woodward CLN, Hall AM, Williams IG, Madge S, Copas A, Nair D, et al. Tenofovir-associated renal and bone toxicity. HIV Med (2009),. 2009;10:482–7.

26. Fux CA, Simcock M, Wolbers M, Bucher HC, Hirschel B, Opravil M, et al. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. Antivir Ther. 2007;12:1165–73.

27. Woratanarat K, Talerngsak Kanjanabuch CS. Tenofovir Disoproxil Fumarate-Associated Nephrotoxicity in HIV-Infected Patients : A Prospective Controlled Study. Med Assoc Thai. 2013;96(4):432–9.

28. Shan C, Yin GQ, Wu P. Efficacy and safety of Tenofovir in a kidney transplant patient with chronic hepatitis B and nucleos (t) ide multidrug resistance : a case report. J Med Case Rep. 2014;8(1):1–6.

29. Federal Democratic republic of ethiopia. Country progress report on HIV/AIDS. 2014;

30. Alemu YA. Scaling up Antiretroviral Treatment and Retaining Patients in Care in Resource-limited Settings : Lessons from Ethiopia , 2006-2012. Brussels Univ Press. 2013;2006–12.

31. Bartlett JA, Shao JF. Successes , challenges , and limitations of current antiretroviral therapy in low-income and middle-income countries Barriers to ART. Lancet Infect Dis. Elsevier Ltd; 2009;9(10):637–49.

32. Leon Regensberg CW. Aid for AIDS Clinical Guidelines,south africa. 2010;8:52.

33. World Health Organization. Monitoring for renal toxicity in people receiving tenofovir and on tenofovir toxicity and how it affects disability-adjusted life-years and quality-adjusted life-years Contents,systemati review. Basel Univ Hosp ,switzerl. 2014;1–19.

34. Omeje I OC. Effectiveness and safety of first-line tenofovir + emtricitabine + efavirenz for patients with HIV (Review) Summary of findings for the main comparision. cochraine Libr. 2012;(2).

35. Thuppal S. Treatment of HIV with Zidovudine versus Tenofovir containing regimens in INDIA. thufts Univ. 2012;

36. Campbell TB, Smeaton LM, Kumarasamy N, Flanigan T, Klingman KL, Firnhaber C, et al. Efficacy and Safety of Three Antiretroviral Regimens for Initial Treatment of HIV-1 : A Randomized Clinical Trial in Diverse Multinational Settings. PLoS One. 2012;9(8).

37. Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. Tenofovir Disoproxil Fumarate, Emtricitabine, and Efavirenz Compared With Zidovudine/Lamivudine and Efavirenz in Treatment-Naive Patients 144-Week Analysis. J Acquir Immune Defic Syndr. 2008;47:74–8.

38. Joel E. Gallant, Edwin DeJesus, José R. Arribis, Anton L. Pozniak, Brian Gazzard, Rafael E. Campo, Biao Lu, Damian McColl, Steven Chuck, Jeffrey Enejosa, John J. Toole and AKC. Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV. N ENGL J MED. 2006;354(3):251–60.

39. Labarga P, Barreiro P, Martin-carbonero L, Solera C, Medrano J, Rivas P, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. AIDS2009. 2009;23(6):689–96.

40. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in Renal Function Associated with Tenofovir Disoproxil Fumarate Treatment , Compared with Nucleoside Reverse-Transcriptase Inhibitor Treatment. Clin Infect Dis. 2005;40:1194–8.

41. Velen K, Lewis JJ, Charalambous S, Grant AD, Churchyard GJ, Hoffmann CJ. Comparison of Tenofovir , Zidovudine , or Stavudine as Part of First-Line Antiretroviral Therapy in a Resource- Limited-Setting : A Cohort Study. PLoS One. 2013;8(5):4–11.

42. Bereket Damtew, Bezatu Mengistie Alemayehu and T. Survival and Determinants of Mortality in Adult HIV/AIDS Patients Initiating Antiretroviral Therapy in Somali Region, Eastern Ethiopia. J AIDS Clin Res. 2014;05(07):5–10.

43. Seleke R. A comparison of treatment response in two cohorts of once daily HAART and twice daily HAART in a sample population in Gaborone, Botswana. Stellenbosch Univ http//scholar.sun.ac.za. 2012;

44. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the Highly Active Antiretroviral Therapy Era: Changing Causes of Death and Disease in the HIV Outpatient Study. J Acquir Immune Defic Syndr. 2006;43(1):27–34.

45. Giboux J-M. Getting a head of the wave :Lessons for the Next Decade of the AIDS Response. 2011;

46. Europian AIDS clinical society. gudelines version 7. 2013;0–81.

47. Eluwa GI, Badru T, Akpoigbe KJ. Adverse drug reactions to antiretroviral therapy (ARVs): incidence , type and risk factors in Nigeria. BMC Clin Pharmacol. BioMed Central Ltd; 2012;12(1):7.

48. EHNRI. Survey in HIV drug resistance (HIVDR) early warning indicators (EWIs). HIVDR EWI. 2012;

49. Jimma University specialized hospital; services given in the hospital. 2015.

50. Bastard M, Soulinphumy K, Phimmasone P, Saadani AH, Ciaffi L, Communier A, et al. Women experience a better long-term immune recovery and a better survival on HAART in Lao People ' s Democratic Republic. BMC Infect Dis. 2013;13(27):9.

51. WHO. Patient monitoring guidelines for HIV care and antretroviral therapy (ART). 2006. p. 101.

52. Luguterah MA and A. CD4 + Cell counts of HIV-1 patients on Antiretroviral therapy(ART) in the Builsa district hospital. Eur Sci J. 2013;9(33):299–309.

53. FMoH. Stavudine replacement strategy. 2013;1–14.

54. Samuel Opondo Muhula, Memiah Peter, Biadgilign Sibhatu, Ndirangu Meshack KL. Effects of highly active antiretroviral therapy on the survival of HIV-infected adult patients in urban slums of Kenya. PAJ. 2015;20(63):1–9.

55. Muzah BP, Takuva S, Maskew M. Risk factors for discordant immune response among HIV-infected patients initiating antiretroviral therapy : A retrospective cohort study. S Afr HIV Med. 2012;13(4):168–72.

56. Nakanjako D, Kiragga A, Ibrahim F, Castelnuovo B, Kamya MR, Easterbrook PJ. Sub-optimal CD4 reconstitution despite viral suppression in an urban cohort on Antiretroviral Therapy (ART) in sub-Saharan Africa: Frequency and clinical significance. AIDS Res Ther. 2008;5(23):1–9.

57. Joseph T.Dipiro, Robert L.Talbert, Gary C.Yee, Gary R.Martzke BGW and LMP. Pharmacotherspy,A pathophysiolgic approach. Ninth edit. 2014. 20488 p.

58. Richard E.Chaison and Richard D.Moore. Prevention of Opportunistic Infections in the Era of Improved Antiretroviral Therapy. AIDS Hum Retrovirology. 1997;16(1):14–22.

59. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). Indian J Med Res. 2011;134:866–77.

60. Solomon Hambisa Ejigu, Wote Amelo Rike MTA. Medication adherence and associated factors among patients on highly active antiretroviral therapy in. Gaziantep Med J. 2014;20(3):199–208.

61. Jayant V.Deshpande and Sudha G.Purohit. Life lime Data : Statistical Models and Methods. 2005. 6 p.

62. Alemu AW, Sebastia MS. Determinants of survival in adult HIV patients on antiretroviral therapy. Glob Health Action. 2010;3(5398):1–10.

63. Ralf Weigel, Janne Estill, Matthias Egger, Simon Makombe, Hannock Tweya AJ and OK. Mortality and loss to ollow-up in the first year of ART :Malawi National ART programme. AIDS. 2012;26(3).

64. Johannessen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, Aglen HE, et al. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. 2008;10:1–10.

65. Otwombe KN, Petzold M, Modisenyane T, Martinson NA, Chirwa T. Factors associated with mortality in HIV-infected people in rural and urban South Africa. Glob Health Action. 2014;1(7):1–10.

66. Malini B.Desilva, Stephen P.Merry, Philip R fischer, James E.Rohrer, Christian O.Isichei and SSC. Youth,unemployment,and male gender predict mortality in AIDS patients started on HAART in Nigeria. 2010;21(1):70–7.

67. Stephanus Komati, Pamela A. Shaw, Nomso Stubbs, Monkwe Jethro Mathibedi, Lizette Malan, Phumelele Sangweni, Julia A. Metcalf, Henry Masur and SH. Tuberculosis Risk Factors and Mortality for HIV Infected Persons Receiving Antiretroviral Therapy in South Africa. AIDS. 2010;24(12):1849–55.

68. Stephen D. Lawna, Anthony D. Harries Xavier Anglarete, Landon Myerg and R, WooD. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS. 2012;29(6):997–1003.

69. Kassa NAM and GM. Prevalence of Opportunistic Infections and Associated Factors among HIV Positive Patients taking Anti-Retroviral Therapy in DebreMarkos Referral Hospital, Northwest Ethiopia. J AIDS Clin Res. 2014;05(05):1–6.

70. Madec Y, Laureillard D, Pinoges L, Prak N, Ngeth C, Moeung S, et al. Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. AIDS. 2007;21:327–59.

71. Michael O Iroezindu, Eugenia O Ofondu HH and BVW. Prevalence and Risk Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria. AIDS Clin Res. 2013;S3:1–9.

72. Michael O Iroezindu, Eugenia O Ofondu HH and BVW. Prevalence and Risk Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria. J AIDS Clin Res. 2013;S3:1–9.

73. Zhou J, Sirisanthana T, Kiertiburanakul S, Chen YA, Han N, Lim PL. Trends in CD4 counts in HIV-infected patients with HIV viral load monitoring while on combination antiretroviral treatment : results from The TREAT Asia HIV Observational Database. BMC Infect Dis. BioMed Central Ltd; 2010;10(1):361.

74. Leport C, S, Grabar, Le Moing V, Goujard C, Kazatchkine MD, Costagliola D WL. Clinical outcome of patientswith HIV-1infection according to immunologic and virologic response after. AnnIntMed. 2000;133(6):401410.

75. Janaina Aparecida Schineider Csotti, Luciana Neves Passos FJP de O& CCJ. Prevalence of discordant immunologic andvirologic response in patients with AIDS under HAART in specialized care center in Brazil. Rev Inst Med Trop. 2011;53(6):301–7.

76. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, et al. Characteristics , Determinants , and Clinical Relevance of CD4 T Cell Recovery to < 500 Cells / mm3 in HIV Type 1 – Infected Individuals Receiving Potent Antiretroviral Therapy. Clin Infect Dis. 2005;41(1):361–72.

77. Schechter M, Tuboi SH. Discordant immunological and virological responses to antiretroviral therapy. J Antimicrob Chemother. 2006;58:506–10.

78. Teixeira Â, Valdez H, Mccune JM, Koup RA, Badley AD, Hellerstein MK, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. J Acquir Immune Defic SyndrAIDS. 2001;15(14):1749–56.

79. Lubyayi L, Shkedy Z, Mwehire D, Kawuma E, Odiit M, Mukasa B, et al. Evolution of CD4 Cell Counts over Time for HIV / AIDS Patients on Antiretroviral Therapy (ART) In Mildmay. Biometrics Biostat Int J. 2015;2(2).

80. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract The Journal of Experimental Medicine. 2004;200(6).

81. WHO. Guideline on when to start Antiretroviral Therapy and on pre-exposure prophylaxis for HIV. 2015. 24 p.

82. Suely H. Tuboi, Martin W. G. Brinkhof, Matthias Egger, Roslyn A. Stone, Paula Braitstein, Denis Nash, Eduardo Sprinz, Francxois Dabis, Lee H. Harrison and MS. Discordant Responses to Potent Antiretroviral Treatment in Previously Naive HIV-1 – Infected Adults Initiating Treatment in Resource-Constrained Countries. J Acquir Immune Defic Syndr. 2007;45(1):52–9.

83. Jason V. Baker, Grace Peng, Joshua Rapkin, David Krason, , Cavan Reilly, Winston P. Cavert, Donald I. Abrams, Rodger D. MacArthur, Keith Henry, and JDN. Poor initial CD4+ recovery with HAART prolongs immune depletion and incresase risk of AIDS and non-AIDS disease. J Acquir Immune Defic Syndr. 2013;48(5):541–6.

84. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006;354:251–60.

ANNEXES

ANNEX I: Data collection check list

Jimma University

College of Medical sciences: Department of Pharmacy

Dear,

This data collecting format is prepared to collect data on ***"Treatment outcome assessment of Tenofovir and Zidovudine based regimens among Peoples living with HIV/AIDS at Jimma University Specialized Hospital, ART clinic".***

This study is conducted as part of my MSc thesis in collaboration with Jimma University School of graduate studies. The aim of the study is to assess the treatment outcomes of TDF and AZT based regimens among PLWHA at JUSH. The finding of this study will help in identifying the safest regimen interms of its good treatment outcomes in this specific population group. The information extracted from patients' medical record was kept confidential and not exposed to other parties.

Data collector

Name…….

Sign……

Phone number……

Supervisor

Name……..

Sign……

Phone number……

Instruction

A.Select your answer for the questions by marking "√" in the box provided

B.If your answer is out of the choice provided; write it in the space provided

Part I: Socio-demographic data **Card No.**_____

201	Sex	Male ☐ Female ☐
202	Age(in years)	
203	Educational level	Illiterate ☐ Primary ☐ Post-primary[9th and above] ☐
204	Area of residence	Urban ☐ Rural ☐
205	Habit of social drugs use	Smoking status smoker ☐ non-smoker ☐
		Alcoholic status: Drinker ☐ Non-drinker ☐
206	Occupation	Employed ☐ unemployed ☐ Housewife ☐ Others ,Specify_____
207	Marital status	Single ☐ Married ☐ Divorced ☐ Widowed ☐

Part II: patient's clinical data

<table>
<tr><td>301</td><td>ART initiation date</td><td colspan="4">____/____/_____ (dd/mm/yyyy)</td></tr>
<tr><td>302</td><td>ART initiation</td><td>Age</td><td>Baseline CD4+ count</td><td>WHO clinical stage [I,II,III,IV]</td><td>Functional status(W,A,B)</td></tr>
<tr><td>303</td><td>Patient on prophylaxis</td><td colspan="4">No ☐ Yes ☐
if Yes,
<table><tr><th>Drug for prophylaxis</th><th>Date treatment started</th><th>Medications</th></tr><tr><td>INH</td><td>----/----/----</td><td></td></tr><tr><td>Cotrimoxazole</td><td>----/----/----</td><td></td></tr></table></td></tr>
<tr><td>304</td><td>ART regimen</td><td colspan="4">[1e]☐ [1f]☐ [1c] ☐ [1d] ☐</td></tr>
<tr><td>305</td><td>Comorbidity</td><td colspan="4">Yes ☐ No ☐
If yes,_____(mention)</td></tr>
<tr><td>306</td><td>[BMI in Kg/m^2],if recorded already</td><td colspan="4"></td></tr>
</table>

BMI=body mass-index body mass

Part III-follow-up data documentation chart

Month on ART	Wt. (kg), Ht.(cm)	Functional status(W,A,B)	WHO stage	CD4+ count	OI prophylaxis	TB prophylaxis	ARV drugs		OI	Patient status	
							Dispensed regimen	Adherence (G,F,P)		live	dead

Key: The chart and its parts are designed and filled as per the country's format(s) of HIV/ART follow up form.

Part-IV. List of Codes

The following code was used to fill the questionnaire

OI codes

1. Zoster
2. BP, bacterial pneumonia
3. Pulmonary TB
4. Extra Pulmonary TB
5. Thrush - oral, vaginal
6. Ulcer – mouth, genital
7. Diarrhea chronic/acute
8. Pneumocystis carinii pneumonia
9. CT, CNS toxoplasmosis
10. CM, Cryptococcal meningitis
11. Others

Functional status

- W= working
- A= ambulatory
- B= bedridden

Adherence

- G= good
- F= fair
- P= poor

Follow up date

- **0=ART initiation date**
- **1w= one week**
- **1m= one month**

Side Effects

1. Nausea
2. Diarrhea
3. Fatigue
4. Head ache
5. Rash
6. Anemia
7. Abdominal pain
8. Jaundice
9. Dizzy, anxiety, night mare

Dispensed Regimen

1c= AZT-3TC-NVP
1d= AZT-3TC- EFV
1e= TDF-EMC- NVP
1f= TDF-EMC- EFV

DECLARATION

This is to certify that the paper prepared by Teshale Ayele, entitled: "Treatment outcomes of Tenofovir and Zidovudine-based regimens among people living with HIV/AIDS at Jimma University Specialized Hospital, Southwest Ethiopia" in partial fulfillment of the requirements for the degree of Master of Science in Clinical Pharmacy. I declare that this paper is original work and all sources of material used for this thesis and peoples involved are fully acknowledged.

Name: Teshale Ayele

Signature_____ Date _____

Approved by:

1st advisor's Name: Girma Mamo

Signature _____ Date_____

2nd advisor's Name: Habtemu Jarso

Signature _____ Date_____