RATE OF INITIAL ANTI-RETROVIRAL TREATMENT MODIFICATION AND ITS PREDICTORS AMONG ADULT HIV/AIDS PATIENTS AT PAWE GENERAL HOSPITAL, BENISHANGUL GUMUZ REGION, NORTHWEST ETHIOPIA

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Abstract

Background: Combination antiretroviral therapy (cART) is the cornerstone of managing patients with HIV infection. Once cART is initiated, patients generally remain on medications indefinitely. However, antiretroviral regimens commonly require changes which often involve switches of multiple medications simultaneously. The maximal regimen durability with regard to safety and efficacy is a critical factor for long-term success of ART since modification to cART has a number of challenges.

Objectives: To assess the rate, time to change, reasons and predictors of treatment modification among HIV/AIDS patients at Pawe General Hospital.

Method: Hospital based retrospective cohort study was conducted among adult HIV/AIDS patients on follow-up in Pawe Hospital from 01 April 2017 to 30 April 2017. Patients who started cART at Pawe General Hospital from January 2012 to December 2016 were included. Data abstraction tool was used to collect data from patient chart. Data were analyzed using SPSS version 21. Descriptive statistics were used to summarize patient socio-demographics characteristics and rate of regimen modification. Bivariate and multivariate Cox proportional hazard were performed to identify the predictors.

Result: Over a median follow-up period of 21 months (IQR 6 - 38), 62 (14.5%) patients modified their initial regimens (incidence rate (IR); 7.66 per 100 person years [95% CI: 5.84 – 9.50]). Toxicity was the most common reason (72.6%). In multivariate Cox regression model, WHO stage III/IV at initiation (AHR; 2.39, 95% CI: 1.23 – 4.66), AZT based initial NRTI backbone (AHR; 8.19, 95% CI: 4.55 - 14.73), low baseline hemoglobin ((< 7 g/dl [AHR; 6.32, 95% CI: 1.40 – 28.58] and 7-9.9 g/dl [AHR 4.21, 95% CI: 1.92 - 9.22]) and co-medication with cART (AHR 1.73, 95% CI: 1.03 - 2.89) were associated with increased risk of treatment modification.

Conclusion: Initial regimen modification rate was lower in this population than cohorts in resource-rich settings. Toxicity was the most common reason for modification and WHO stage III/IV, AZT based regimen, low baseline hemoglobin and co-medication with cART were found to be predictors of regimen modification.

Key words: Rate, HIV/AIDS, treatment modification, Pawe

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List of Acronyms and Abbreviations

ABC: Abacavir

ADRs: Adverse Drug Reactions

AHR: Adjusted hazard ratio

AIDS: Acquired Immunodeficiency Syndrome

ART: Antiretroviral Therapy

ARV: Antiretroviral

ATV/r: Atazanavir/ritonavir

AZT: Zidovudine

3TC: Lamivudine

EFV: Efavirenz

ART: Antiretroviral Therapy

cART: Combination Antiretroviral Therapy

HIV: Human Immunodeficiency Virus

INH: Isoniazid

IQR: Inter quartile range

LPV/r: Lopinavir/ritonavir

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors

NRTI: Nucleoside Reverse Transcriptase Inhibitors

NVP: Nevirapine

PMTCT: Prevention of Mother to Child Transmission

TB Tuberculosis

TDF: Tenofovir

WHO: World Health Organization

ZDV: Zidovudine

1. Introduction

1.1 Back ground

HIV/AIDS continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2015, 1.1 million people died from HIV-related causes globally. There were approximately 36.7 million people living with HIV at the end of 2015 with 2.1 million people becoming newly infected with HIV in 2015. Sub-Saharan Africa is the most affected region, with 25.6 million people living with HIV in 2015 which accounts for two-thirds of the global total of new HIV infections. It is estimated that currently only 60% of people with HIV know their status. The remaining 40% or over 14 million people need to access HIV testing services (1).

According to single point HIV related estimates and projections for Ethiopia 2016, the national HIV prevalence is 1.1%. The cART began in Ethiopia in 2003 and free antiretroviral therapy (ART) was launched in 2005. An estimated 718,500 Ethiopians are currently living with HIV, of whom 542,600 require cART and 367,000 are currently taking the treatment in which coverage for adults (age 15+) has reached 76% (2).

The treatment of human immunodeficiency virus (HIV) infection has been revolutionized by potent antiretroviral therapy. Use of these multidrug regimens has resulted in substantial reductions in progression to AIDS, opportunistic infections, hospitalizations, and deaths (3). Combination antiretroviral therapy (cART) is the principal approach for preventing immune deterioration. With rare exception, all HIV infected individuals with detectable viremia, regardless of their CD4 cell count, should begin antiretroviral therapy as soon as possible after diagnosis to prevent disease progression, improve clinical outcomes, and limit transmission (4). Excess mortality among HIV-infected persons has decreased dramatically since the introduction of cART (5).

The cART is the cornerstone of management of patients with HIV infection and its initiation should be timed appropriately and not delayed until the immune system is irreversibly damaged. Since the goal of cART is to attain maximal and durable suppression of the viral replication, its effectiveness is assessed by clinical observations, CD4 cell count and determination of plasma viral load(6). Therefore, sustained viral suppression, restoration of immunologic function,

reduction of HIV related morbidity and mortality, improvement of quality of life and prolong survival has become an integral part of the continuum of HIV care (7).

Triple combination therapy has been in use for more than two decades globally. Currently, the preferred first-line ART regimen in Ethiopia for adults including pregnant and breast feeding women and adults with TB co-infection is TDF/3TC/EFV. The alternative first line regimens are TDF/3TC/NVP, ZDV/3TC/EFV and ZDV/3TC/NVP. The second line regimen consists of TDF+3TC+LPV/r or ATV/r, ZDV+3TC+LPV/r or ATV/r (2).

Once cART is initiated, patients generally remain on medications indefinitely. However, antiretroviral regimens commonly require changes which often involve switches of multiple medications simultaneously. This is often necessary because of the risk of acute toxicity, long-term toxicity, treatment failure, poor adherence, a desire for pregnancy, comorbidity with other chronic diseases or stock out of drugs (8). The approach depends on the reason for change, the amount of previous cART experience, and the available treatment options (8, 9).

The maximal regimen durability with regard to safety and efficacy is a critical factor for long-term success of ART (10). Modification to cART has a number of challenges such as limited therapeutic alternatives, cross-resistance between possible alternatives, and overlapping of toxicity between potential alternatives, adherence and quality of life challenges (11). In sub-Saharan Africa, where drug options are limited due to limited resources, regimen durability takes on more important role than in industrialized countries. It becomes imperative to carefully select cART regimen at initiation and understand the determinants of regimen change in order to ensure treatment success (12).

Most patients tolerate their initial treatment regimens well for up to 24-36 months after initiation. However, a significant number of patients' treatment regimens are modified for various reasons (13, 14). Strategies to maximize drug tolerability from the available first line regimens are vital in resource limited settings where subsequent treatment options are limited. In order to achieve this goal, it is important to understand the reasons for changes in cART regimens and the risk factors that may be associated with a need for treatment modification. Such an understanding will help to individualize drug regimens that are better tolerated among patients at the same time preserving future treatment options (15).

There are limited data on the magnitude and predictors of cART regimen modification in Ethiopia especially in the study area, where there has been rapid scaling up of ART services over the past decade. In this study, the aim is to determine the magnitude and reasons of modification of first-line cART among HIV infected patients who initiated cART at the Pawe General Hospital as well as to identify baseline demographic and clinical characteristics that predict first-line regimen modification.

1.2 Statement of the problem

The current status of antiretroviral therapy is encouraging, but significant challenges remain and treatment outcomes continue to be substantially worse (16). Even though cART inhibits viral replication, it may cause a number of adverse effects; which may end with treatment failure and/or regimen changes (17).

The cART switching/modification is associated with economic outcomes and certain adverse treatment effects. Efforts to put patients on an optimal cART regimen initially may have a positive effect on patients and the health care system by reducing the need for subsequent switching (18). Modification of cART presents a number of challenges such as limited therapeutic alternatives, viral cross-resistance between possible alternatives, and overlapping of toxicity between potential alternatives, in addition to adherence and quality-of-life challenges (11).

Successive regimens are inferior to that of the original regimen in related to effectiveness and duration. In addition, regimen change result in a number of challenges, reduce both the duration and the chance of viral control due to cross resistance between different alternative drug and overlapping toxicity between and within a class of antiretroviral (ARV) drug. The likelihood that successful cART will last life time is poor and also second line cART is more expensive than that of first line cART. Patients failed on the first line drug are 46% more likely to fail again on the second line drug & attributed to the higher number of side effects, have greater likelihood of experiencing drug resistance as a result of being on treatment longer (19, 20).

Clinical factors such as, low CD4 counts at treatment initiation, co-infection, and treatment initiation at late stage of the disease have also been implicated in cART modification and these factors are more common in stigmatized population or where patient support facilities are inadequate (21).

The frequency of treatment modification reported in resource limited setting is high ranging from 8.3 to 78.4% for switch (15, 22-24). The reported high levels of treatment modification may pose a challenge to treatment programs impacting on the overall cost of cART and limiting good patient prognosis. Due to these constraints maximizing the duration of patients on initial first-line regimen and optimizing the use of well-tolerated drugs are important (17-19).

Similarly in Ethiopia the magnitude and pattern of regimen change is also high with reported 20% in Mekele hospital (25). There is also a reported overall incidence rate of initial regimen change from Gondar hospital which is 10.11 per 100 person years that is encountered due to different reasons for the change (26).

Research conducted on modification of cART and factors associated with antiretroviral drug switch among HIV patients are limited in Ethiopia. Even though, there are some researches done regarding pattern of antiretroviral drug switch and the associated reasons for the switch, the studies on predictors of the treatment modification are limited.

1.3 Significance of the study

The current policy on ART in Ethiopia aims at consistent provision of cART and close monitoring of patients to ensure continued sustenance of patients on a potent first line regimen. Designing strategies to increase the durability of first regimen is essential in developing countries like Ethiopia, where limited options are available. The existence of multiple reasons for cART modifications calls for a holistic approach in the elucidation of preventable factors associated with these outcomes.

The cART modification results in poor treatment outcome and exposes patients to resistance. This demands understanding of the magnitude and its predictors. Even though there are researches done regarding the reasons for cART regimen change in Ethiopia, the predictors for regimen modification are not well studied. In addition, there is no research done on the magnitude and predictors in the study area. Therefore, it is important to evaluate the rate and predictors of cART regimen change.

The findings from this study will have an input in understanding the magnitude and identifying risk factors of cART regimen change. This helps in designing appropriate measures to increase the duration of initial regimen which preserves the future treatment options. Finally, information regarding the rate and time to treatment modification could be used for projection purposes in assessing the long-term success of treatment programs.

2. Literature review

2.1 Prevalence, Reasons and Pattern of cART regimen change

A large prospective cohort study with continuous enrollment of HIV-infected individuals in 1318 antiretroviral-naive HIV–infected individuals from the Swiss HIV Cohort Study showed that the total rate of treatment modification was 41.5 per 100 person years. Of these, switches of regimen occurred at a rate of 22.4 per 100 person-years because of drug toxicity. The most frequent toxic effects were gastrointestinal tract intolerance (28.9%), hypersensitivity (18.3%), central nervous system adverse events (17.3%), and hepatic events (11.5%) (27).

In an observational cohort study conducted in Northern Thailand, the event of regimen modification corresponds to an incidence of 13.8/100 person-year-observation over 2,728 person years follow up. The main reasons for regimen modification were adverse effects (73.5%), especially lipodystrophy (63.2%) followed by rash (17.7%). Also 17.1% of patients changed the regimen due to treatment failure. Female gender and elder age were protective for treatment failure related modification (28).

A study in Southern India also showed that, 20% of patients modified their first-line regimen during evaluation of cART–naive patients who initiated cART and had at least one follow-up visit. The most common reason for modifying therapy was the development of an adverse effect (64%), followed by cost (19%) and treatment failure (14%), with median times to modify therapy being 40, 151, and 406 days, respectively. Common adverse effects were itching and/or skin rash (66%), hepatotoxicity (27%), and anemia (23%) (29).

According to institutional based retrospective follow up study conducted at the University of Gondar Referral Hospital among adult HIV patients showed that, 21.5% of patients were changed their initial regimen. This makes the overall rate of initial cART regimen change found to be 10.11 per 100 person years. Among the reasons for regimen change, side effect was the commonest reason which accounts for 70.45 % of cases and contribute for the 7.13/100 person years. Tuberculosis 20.45 %, pregnancy 4.5 %, virological failure 3.4 % and occurrence of hepatitis B with chronic liver diseases 1.14 % were other reasons for regimen change. The commonest side effect for regimen change was found to be anemia (53.2 %), followed by rash (22.6 %) (26).

In Adama Hospital Medical College retrospective cross-sectional study was done by reviewing patient information cards recorded from June 1, 2010 to June 1, 2014. The most common reasons for modification of regimen were toxicity (70%), co-morbidity (12.7%), pregnancy (10%) and treatment failure (7.3%). The main types of toxicities observed were peripheral neuropathy (30.5%), lipoatrophy (18.1%) and anemia (17.1%). The result of this study indicated toxicity as the main reason for modification of initial antiretroviral drugs among the study population(30).

A retrospective cross sectional study done in Nekemt Hospital also showed that, the main reasons for modification of therapy were toxicity (80.3%), pregnancy (6.3%), new TB (5.6%), stock out (4.9%) and treatment failure (2.8%). The main toxicity observed was lipoatrophy (58.8%) followed by rash (12.3%) and CNS toxicity (11.4%). Toxicity was the main reason for initial regimen modification. D4T based regimens had high incidence of lipoatrophy (31). Similarly, a study in Fiche Hospital shows that the main reason for regimen change was toxicity (72.73%) followed by treatment failure (14.23%), new drug available (9.09%), co morbidity (2.60%), and (1.30%) patient refused to took the drug. From all the toxicities reported, lipoatrophy, which accounted for 73.47% of the toxicities, was the most common. Toxicity appears as the main reason for treatment and regimen change in this study (17).

2.2 Contributing factors of Regimen change

In the multivariate analysis of Swiss HIV Cohort Study, combined zidovudine and lamivudine, nevirapine, comedication for an opportunistic infection, advanced age, female sex, nonwhite ethnicity, higher baseline CD4 cell count, and HIV-RNA of more than 5.0 log10 copies/mL were associated with higher rates of treatment modification (27).

A retrospective research done in Nigeria on patients initiated first-line cART indicated that 83% of patients incurred a modification (73.3% drug substitution and 9.7% drug switch) to their initial first-line ARV regimen during a median follow-up period of 7 years. Predictors of switch to second-line regimen include older age, CD4 count ≤100 cells/mm3, and drug toxicity (32).

A study conducted in Keniya showed that, the prevalence of cART switch is 54.5% and the cumulative incidence of cART switch at 12 months was 78.4%. The presence of concurrent cART-related toxicities (40.6%) and TB treatment interactions (28.1%) were the most frequent reasons for cART switch while baseline AIDS symptoms and a CD4 count ≤100 cells/mm3 were

independent predictors of cART switch. The most frequently (20.7%) reported toxicity was peripheral neuropathy while a CD4 count ≤100 cells/mm3 was an independent predictor of clinical toxicity (24). In another study 18.7% of patients modified regimens and toxicity was the most common reason (66.3%). WHO disease stage III/IV, stavudine (d4T) use and increase in age were associated with increased risk of treatment modification within the first year post-cART. Zidovudine (AZT) and tenofovir (TDF) use had a reduced risk for modification. Beyond one year of treatment, d4T use, baseline CD4 counts ≤350 cells/mm3, increase in age and high baseline weight >60kg were associated with risk of cART modification (33).

The findings from case-control study conducted in Mekelle hospital showed that, 20% of the patients had changed their initial cART regimen and about 71.4% of the reasons for change were attributable to toxicity while 14.3% and 9.5% were due to treatment failure and pregnancy respectively. Adverse Drug Reactions (ADRs), ZDV based cART regimen, treatment duration of 12-36 months, use of concurrent drugs up on cART treatment were associated with a higher chance of changing their baseline cART regimen. The main factor determining the change of initial cART regimen in this study was the occurrence of adverse drug reactions, with ZDV being the most dominant drug (25).

Based on the study conducted at Gondar Hospital baseline WHO clinical stage III, occurrence of TB on the initial regimen, side effect on the initial regimen and co-medication with cART were significant predictors of initial regimen change (26).

2.3 Conceptual frame work

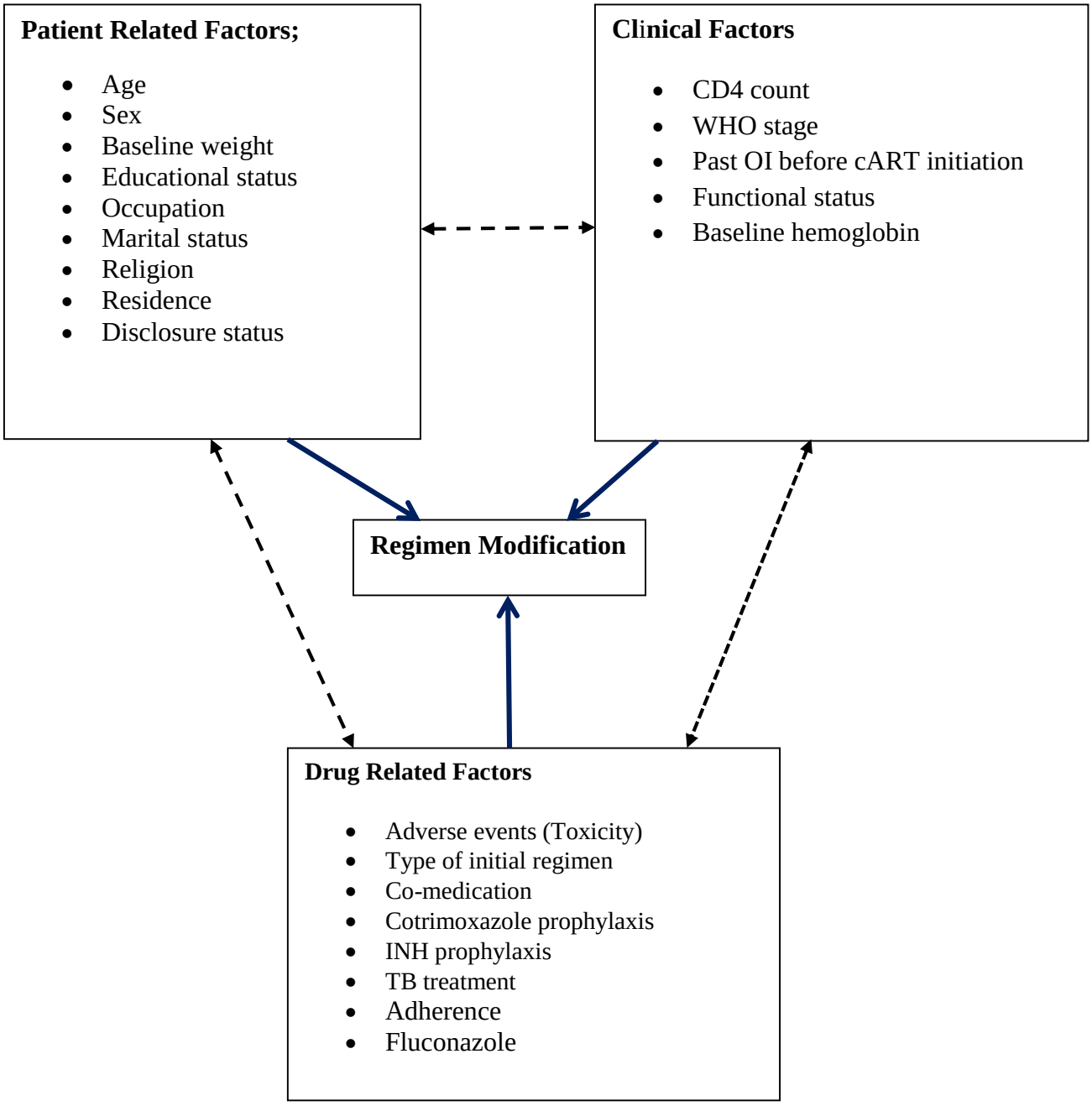

Figure 1 : Conceptual framework showing the relationship between regimen modification and contributing factors (developed after reviewing similar literature).

3. Objective

3.1 General objective

- To assess the rate, time to change, reasons and predictors of initial treatment modification among HIV/AIDS patients at Pawe General Hospital, Benishangul Gumuz region.

3.2 Specific objectives

- To determine the incidence rate of first time cART modification
- To assess the reasons for regimen change
- To determine time to treatment modification
- To identify the predictors associated with first time cART modification

4. Methods and Participants

4.1 Study Period and Study area

The study was conducted at ART clinic of Pawe General Hospital which is one of the two hospitals in Benishangul Gumuz region. Pawe Hospital is a general hospital which serves around four hundred thousand people of the Metekel zone and peoples from the neighboring zones of Amhara region. The HIV care service of the hospital was initiated in 2005 G.C and has 3 outpatient rooms, one voluntary testing and counseling room, one pharmacy, and one laboratory. Currently there are around 875 patients on cART medication in the hospital. The study was conducted from 1st April to 30, 2017 by reviewing the medical record of patients who started cART from January 2012 to December 2016.

4.2 Study Design

Institution based retrospective cohort study was conducted.

4.3 Population

4.3.1 Source Population

All adult HIV infected patients who had been on follow-up at the ART clinic of Pawe General Hospital.

4.3.2 Study population

All HIV infected patients who started cART from January 2012 to December 2016 and fulfill the inclusion criteria

4.3.3 Inclusion and Exclusion Criteria

4.3.3.1 Inclusion Criteria

- All patients aged 15 and above who were started cART at Pawe General Hospital from 1st January 2012 to 31st December 2016 and have at least one follow up visit were included in the study.

4.3.4 Exclusion Criteria

- Patients with incomplete demographic and clinical information.
- Patients who started cART from other health facility and transferred in

4.3.5 Sample Size and sampling technique

The minimum sample size required was calculated using EPI INFO Stat Calc program with the assumption of 95 % level of confidence, 5 % of marginal error and 80% power. From a previous study in Gondar referral hospital patients with WHO stage III at initiation of cART are at increased risk of initial regimen change by 1.92 times when compared to those who were stage I/II (26). Therefore, by using a power of 0.8 a minimum sample size of 342 to detect a minimum hazard ratio of 1.92 of initial regimen change between patients with WHO stage III vs WHO stage I/II was required. But in order to increase the power of this study all eligible patients who had started cART from January 2012 to December 2016 were taken as a sample and the charts of all patients with in this study period were reviewed.

4.4 Study variables

4.4.1 Dependent variables

- ✓ Regimen modification

Primary outcome: Rate of initial cART modification

The primary outcome of this study was initial cART modification which was defined as the first change of one or more antiretroviral drugs used in the cART regimen.

Secondary outcome: Time to treatment modification, reason for regimen modification

It was calculated as time from treatment initiation to first time cART modification.

4.4.2 Independent variables

Socio-demographic characteristics:

- ✓ Age at initiation
- ✓ Gender
- ✓ Baseline weight
- ✓ Marital status
- ✓ Educational status
- ✓ Religion
- ✓ Occupation
- ✓ Residence
- ✓ Disclosure status

Disease related variables:

- ✓ Baseline WHO stage
- ✓ Base line CD4 count
- ✓ Past OI before cART initiation
- ✓ Functional status
- ✓ Baseline hemoglobin

Treatment related variables:

- ✓ Types of initial regimen
- ✓ Adverse events (Toxicity)
- ✓ Co-medication other than cART
- ✓ Adherence
- ✓ Cotrimoxazole prophylaxis
- ✓ INH prophylaxis
- ✓ TB treatment
- ✓ Fluconazole

4.5 Data collection instrument and procedure

Data abstraction form (Annex I) was developed from baseline socio-demographic, immunologic and clinical as well as treatment related factors collected from different articles done previously and was modified to match with ART follow up record of the setting. The available information on the patient records was first observed and the tool was used to collect the data. The data was collected by two BSc. nurses and two pharmacists who had ART training using the prepared data collection format on the already existing medical records. Identification and picking up the charts was also supported them by one data clerk. Charts were retrieved using the patient registration number which was found in the data base in the electronic system.

4.6 Data Processing, Analysis and Presentation

The data were entered to Epi data version 4.2 and exported to SPSS version 21. Then it was cleaned for inconsistencies and missing values. Descriptive statistics were used to summarize socio-demographic and clinical data as well as rate of treatment modification. The survival analysis was carried out, as this study had considered time-to-event data, Cox proportional hazard model was fitted, and cumulative probabilities of regimen modification was estimated. The Kaplan–Meier curve and Log rank test was used to compare survival experiences between the different categories of the explanatory variables. Bivariate and multivariate Cox proportional hazard model was used to identify the predictors. Variables with p value <0.25 in the bivariate analysis were entered into the multivariate proportional hazard model. The 95 % CI of hazard ratio was computed and variable having p value <0.05 in the multivariate Cox proportional hazards model were considered as significantly and independently associated with the dependent variable.

4.7 Data Quality Management

To ensure data quality, the data collectors were trained by the principal investigator before the data collection. The data abstraction tool was pre-tested on 5% of the sample size at the same facility to check for appropriateness and consistency and the necessary modification was made on the final data extraction format. Frequent checks on the data collection process were made to ensure the completeness and consistency of the collected data. Quality of data was maintained by recruiting data collectors who had taken ART training. The retrieval process was closely monitored by the principal investigator throughout the data collection period. Completed questionnaires were checked regularly for completeness of information and any gaps identified were immediately communicated to the data collectors.

4.8 Ethical Consideration

Before starting the study, ethical clearance was obtained from the Institutional Review Board (IRB) of Jimma University. In addition, permission letter was obtained from the clinical director of the Pawe Hospital to conduct the study. The confidentiality of the patients was maintained by avoiding name and identification number from data extracting and only numerical identifications were used as a reference.

4.9 Dissemination plan

The result of this study will be disseminated to relevant bodies including to the school of pharmacy of Jimma University, Benishangul Gumuz region and for the communities of Pawe Hospital. Attempts will be made to publish on reputable scientific Journal and present the finding on scientific conferences.

4.10 Variable definitions

4.10.1 Operational definitions

Treatment modification: was defined as any change of one or more combination antiretroviral treatment components excluding dosage adjustment.

Initial regimen modification: a switch or substitution of at least one drug from the first cART regimen.

Drug switch: defined as a change from the first-line NNRTI-based to the second-line PI-based ARV regimen.

Drug substitution: defined as the replacement of one or more drugs in the first-line regimen (NRTI or NNRTI) with another drug from the same class (NRTI or NNRTI). Change between 3TC and FTC (or vice versa) is not classified as a drug substitution because these are considered therapeutically interchangeable.

Discontinuation: was defined as stopping any antiretroviral drug for at least 4 weeks.

Censoring: Patients with the first date of lost to follow up, transfer out, death before the end of the follow up period and completed the follow up period without developed the event were considered as censored in this study.

Co-medication: medication taken with cART other than CPT, INH, fluconazole prophylaxis.

Adherence: good: those patients with adherence level with 95% and above.

Fair: patients with having adherence level of 85% -95%.

Poor: those patients having adherence level of less than 85%.

4.10.2 Standard definitions

Treatment failure: defined as either clinical failure, immunological failure or virological failure.

Clinical failure: new or recurrent WHO stage 4 condition

Immunological failure: fall of CD4 count to pre-treatment baseline or below or 50 % fall from the on-treatment peak value or persistent CD4 levels below100 cells/mm3.

Virologic failure was defined as plasma viral load (VL) of above 1000 copies/mL on 2 consecutive VL measurements after 6 to 12 months of cART initiation, with documented optimal adherence (2)**.**

5. Results

A total of 875 patients were enrolled but only 641 patients initiated during this period. A further 213 patients did not meet the eligibility criteria and subsequently 428 subjects were enrolled in the study (***figure 2***).

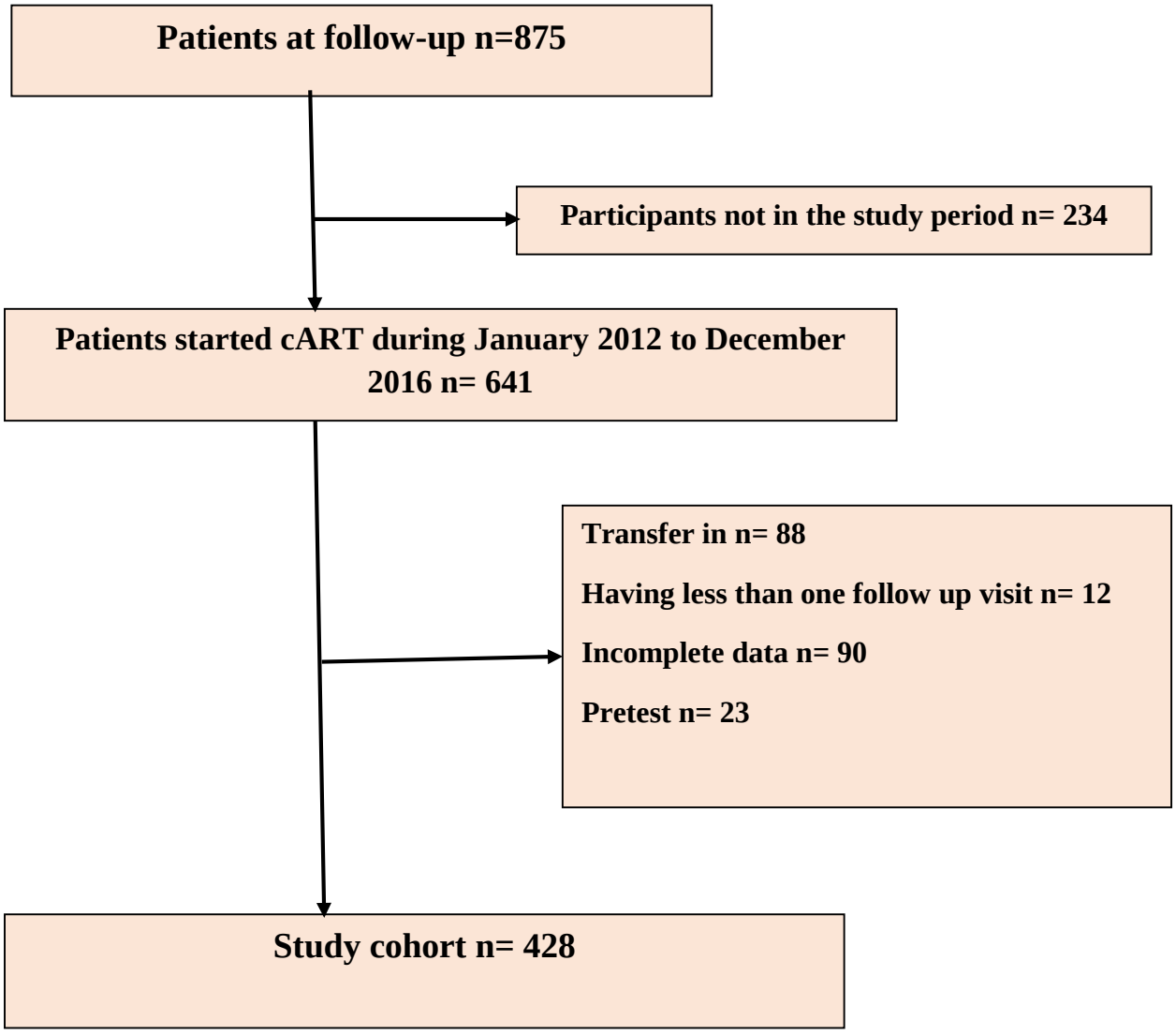

Figure 2: ***Patient enrollment***

5.1 Baseline Characteristics of Study Participants

A total of 428 participants aged 15 years and above who initiated treatment were enrolled in this study and their records were analyzed. The mean age at the initiation of cART was 31.8 ± 8.8 years and 194 (45.3 %) of the participant were in the age group between 25 and 34 years. More than half of the respondents 250 (58.4 %) were female and majority 357 (83.4 %) of them were Orthodox Christian. Regarding the level of education, 125 (29.2 %) of the respondents were completed primary education. More than half 232 (54.2%) of the respondents were married. Nearly half 206 (48.1 %) of the respondents were urban dwellers. A total of 345 (80.6 %) patients had disclosed their HIV status to either their family member or other relatives (**Table 1**).

Table 1 Baseline socio demographic characteristics of HIV positive adults at initiation of cART at Pawe General Hospital, January 2012 to December 2016 (n = 428)

Variable	Category	Frequency	Percentage (%)
Gender	Male	178	41.6
	Female	250	58.4
Age (in years)	15-24	75	17.5
	25-34	194	45.3
	35-44	114	26.6
	45-54	36	8.4
	≥55	9	2.1
Marital status	Married	232	54.2
	Divorced	78	18.2
	Single	62	14.5
	Separated	31	7.2
	Widowed	25	5.8
Educational status	No formal education	205	47.9
	Primary	126	29.4
	Secondary	70	16.4

	Tertiary	27	6.3
Occupation	Farmer	122	28.5
	House wife	85	19.9
	Daily laborer	78	18.2
	Government employer	74	17.3
	Merchant	51	11.9
	Others	18	4.2
Religion	Orthodox	358	83.6
	Muslim	46	10.7
	Catholic	15	3.5
	Protestant	9	2.1
Residence	Urban	206	48.1
	Rural	222	51.9
Disclosure status	Disclosed	345	80.6
	Not Disclosed	83	19.4

5.2 Baseline clinical and immunological status of the respondents

Nearly half 213 (49.8 %) of the study subjects were WHO clinical stage III at the initiation of the cART. Around 145 (33.9%) of the participants had CD4 count of 200-349 cells/mm3. The median CD4 count at initiation of cART was 243 (IQR 128.25 - 359.75) cells/ mm3. The mean weight of the Participant was 50.86 ± 9.20 kg. Majority 348 (81.3%) of the participants were adherent to their medication and 347 (81.1%) of them were on working functional status at a baseline. The predominant cART regimen initially prescribed for them were a combination of Tenofovir, Lamivudine and Efavirenz (TDF-3TC-EFV), 290 (67.8 %) followed by Zidovudine, Lamivudine and Nevirapine (AZT-3TC-NVP) for 72 (16.8 %) cases. One hundred sixty-nine (39.5%) of the study participants were diagnosed for opportunistic infection before initiation of cART and after confirmation of HIV infection. Majority 332 (77.6%) of participants were started TDF as an initial NRTI backbone and 314 (73.4 %) of them were initiated on EFV based regimen. Fifty-six patients (13.1%) also had tuberculosis and taking anti-TB medications with cART. Around 341 (80%) of the patients were taking the CPT prophylaxis and 235 (54.9%) were taking INH prophylaxis. A total 167 (39%) of the patients were also taking medications other than CPT, INH and fluconazole prophylaxis on top of cART medications. Nearly half, 219 (51.2 %) of study subjects were started cART at hemoglobin level of 10-12.9 g/dl (**Table 2**).

Table 2 Baseline clinical and immunological status of HIV positive adults at initiation of cART, Pawe General Hospital from January 2012 to December 2016 (n = 428)

Characteristics	Category	Frequency	Percentage (%)
WHO clinical stage	stage I	87	20.3
	stage II	102	23.8
	stage III	213	49.8
	stage IV	26	6.1
Baseline CD4 count	<100 cells/mm3	79	18.5
	100-199 cells/mm3	91	21.3
	200-349 cells/mm3	145	33.9
	≥350 cells/mm3	113	26.4
Adherence	Good	348	81.3
	Fair	19	4.4
	Poor	61	14.3
Functional status	Working	347	81.1
	Ambulatory	69	16.1
	bed ridden	12	2.8
Baseline weight	<50 kg	185	43.2
	≥50 kg	243	56.8
Initial cART regimen	AZT/3TC/NVP	72	16.8
	AZT/3TC/EFV	24	5.6
	TDF/3TC/EFV	290	67.8
	TDF/3TC/NVP	42	9.8
Past OI before initiation of cART	Yes	169	39.5
	No	259	60.5
Tuberculosis	Yes	56	13.1
	No	372	86.9

Initial NRTI backbone	AZT	96	22.4
	TDF	332	77.6
Initial NNRTI	NVP	114	26.6
	EFV	314	73.4
CPT prophylaxis	Yes	341	79.7
	No	87	20.3
INH prophylaxis	Yes	235	54.9
	No	193	45.1
Fluconazole prophylaxis	Yes	13	3.0
	No	415	97.0
Co-medication	Yes	167	39.0
	No	261	61.0
Baseline Hemoglobin	<7 g/dl	8	1.9
	7-9.9 g/dl	59	15.7
	10-12.9 g/dl	219	51.2
	≥13 g/dl	142	33.2

OI= opportunistic infection; NRTI= nucleoside reverse transcriptase inhibitor; NNRTI= non-nucleoside reverse transcriptase inhibitors; CPT= co-trimoxazole preventive therapy; INH=isoniazid;

5.3 Rate of Regimen Modification

Four hundred twenty-eight study subjects who were followed for different period gave a total of 9709.47 person months (809.12 person years (PY)) of observation. Within this follow up period, a total of 62 (14.5 %) patients modified their initial regimen. This makes the overall rate of initial regimen modification 7.66/100 PY (95 % CI 5.84 - 9.50). Regarding time to initial regimen modification, 32 (51.6%), 38 (61.3 %) and 57 (91.9 %) changed their regimen within 6 months, 1 year and 3 years respectively. The remaining 5 (8.1 %) changed after 3 years of follow up. The cumulative probability of surviving on initial regimen at the end of 6 months was 0.92; at the end of one years was 0.90; at the end of 3 years was 0.82 and at the end of follow-up was 0.76 (***Figure 3***). The most common reason for regimen modification was toxicity/side effect which accounts about 45 (72.6 %) of the cases and contribute for 5.56/100 PY (95% CI 3.98 - 7.14). Treatment failure 13 (21.0%) and TB 4 (6.5 %) were the other reasons for the regimen modification. The most common side effects for the regimen modification were anemia which accounts 23 (51.1%) of the cases and followed by rash 13 (28.9%), CNS toxicity 7 (15.5%), and renal failure 2 (4.3 %) (**Table 3**).

Table 3 ***Reasons for regimen modification and common side effects among patients with initial regimen modification at Pawe General Hospital (n = 62)***

Characteristics		Frequency	Percentage (%)	Incidence rate [95% CI]
Reason for modification	Toxicity	45	72.6	5.56/100PY [3.98-7.14]
	Treatment failure	13	21.0	1.60/100PY [0.73-2.46]
	Tuberculosis	4	6.5	0.50/100PY [0.01-0.97]
Type of toxicity/ Side effect	Anemia	23	51.1	2.84/100PY [1.69-3.98]
	Rash	13	28.9	1.60/100PY [0.73-2.46]
	CNS toxicity*	7	15.5	0.87/100PY [0.23-1.50]
	Renal failure	2	4.4	0.25/100PY [0.09-0.59]

* CNS=central nervous system; CI= confidence interval; PY= person-years

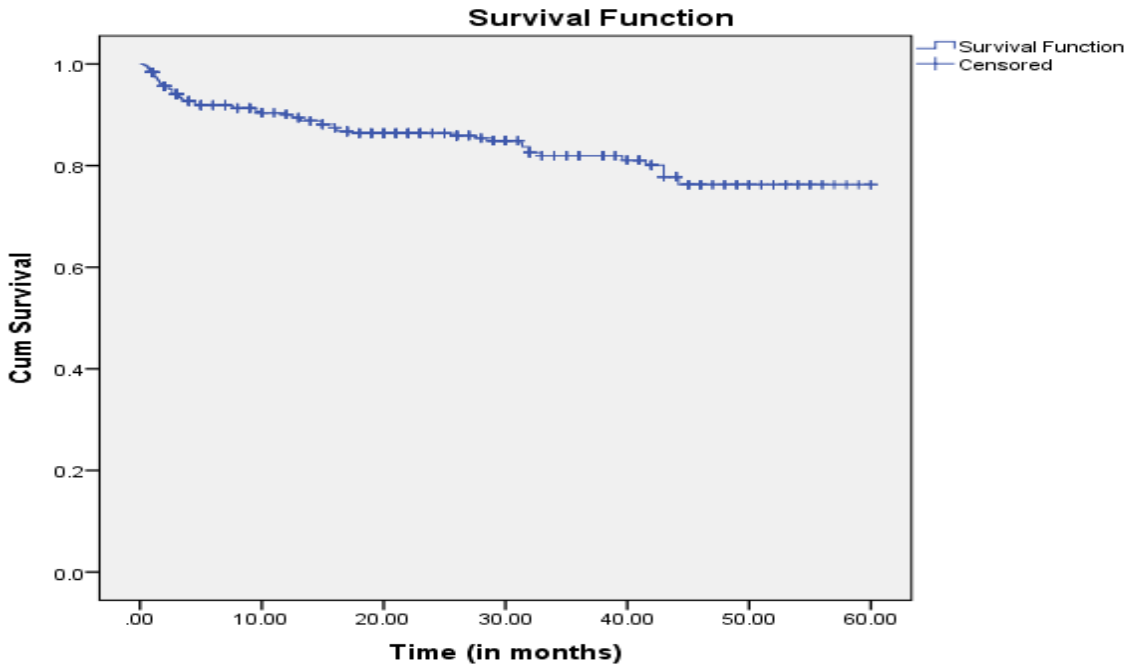

Figure 3 Kaplan-Meir curve of proportion surviving on initial regimen for adult HIV positive patients on initial cART at Pawe General hospital, starting from January 2012 to December 2016

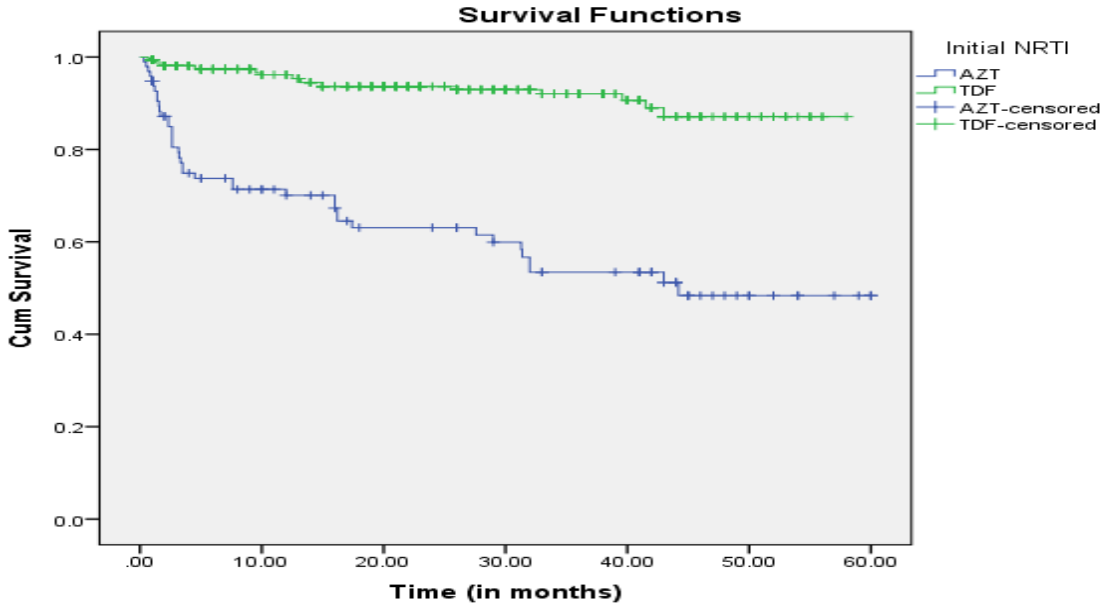

Figure 4 Kaplan-Meier curve of proportion surviving on initial regimen based on NRTI backbone at Pawe General hospital, starting from January 2012 to December 2016

5.4 Predictor of regimen modification

From the covariates included in the model baseline WHO clinical stage, baseline hemoglobin, co-medication with cART, residence, disclosure status, initial NRTI backbone, initial NNRTI, occurrence of TB, and fluconazole prophylaxis were significantly associated with outcome variable at p-value 0.25 in bivariate analysis. Those variables which have p- value less than 0.25 in the bivariate analysis were included in the multivariate model for analysis. In the multivariate Cox-regression analysis (**Table 4**), baseline WHO clinical stage, co-medication with cART, initial NRTI backbone, and baseline hemoglobin of the patient remained a significant predictors of the initial regimen modification. Baseline WHO clinical stage III/IV at cART initiation (AHR 2.39, 95% CI: 1.23 – 4.66), and individuals who initiated cART with AZT as an initial NRTI backbone (AHR 8.19, 95% CI: 4.55 - 14.73) were more likely to experience an initial treatment modification of their cART regimen. There was no statistical association between the use of nevirapine-containing regimens as initial cART regimen and treatment modification. The increased risk of regimen modification among patients taking medications other than CPT, INH and fluconazole prophylaxis with cART were 1.73 times compared with those who did not take other medications (AHR 1.73, 95% CI: 1.03 - 2.89)**.** Patients having low baseline hemoglobin (< 7 g/dl [AHR 6.32, 95% CI: 1.40 – 28.58] and 7-9.9 g/dl [AHR 4.21, 95% CI: 1.92 - 9.22]) were at higher risk for regimen modification compared with those patients with high baseline hemoglobin.

Table 4 Bivariate and multivariable Cox regression analysis for predictors of initial cART regimen modification among adult HIV positive patients at Pawe General Hospital, January 2012 to December, 2016 (n = 428)

Variable		Regimen Modification		Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
		Yes	No				
Gender	Female	36	214	1			
	Male	26	152	1.120 [0.676, 1.856]	0.659		
Age (years)	< 30	30	156	1			
	≥ 30	32	210	0.843 [0.512, 1.387]	0.502		
Marital status	Married	36	196	1			

	Unmarried	26	170	1.240 [0.615, 2.500]	0.548		
Educational status	No formal education	30	175	0.663 [0.276, 1.593]	0.358		
	Primary	16	110	0.525 [0.203, 1.354]	0.183		
	Secondary	10	60	0.805 [0.298, 2.180]	0.670		
	Tertiary	6	21	1			
Occupation	Farmer	13	109	1			
	House wife	13	72	1.284 [0.595, 2.771]	0.524		
	Daily laborer	10	68	1.027 [0.449, 2.348]	0.951		
	Government employed	15	59	1.756 [0.835, 3.691]	0.137		
	Merchant	9	42	1.673 [0.715, 3.917]	0.235		
	Others*	2	16	1.014 [0.229, 4.497]	0.985		
Religion	Orthodox	50	308	1			
	Muslim	9	37	1.647 [0.809, 3.354]	0.169		
	Catholic	2	13	0.905 [0.220, 3.722]	0.890		
	Protestant	1	8	0.864 [0.119, 6.260]	0.885		
Residence	Rural	22	200	1			
	Urban	40	166	**1.759 [1.045, 2.960]**	**0.034**		
Adherence	Good	47	301	1			
	Fair	4	15	2.491 [0.895, 6.931]	0.080		
	Poor	11	50	1.455 [0.755, 2.807]	0.263		
Disclosure status	Disclosed	42	303	1			
	Not disclosed	20	63	**1.925 [1.129, 3.280]**	**0.016**		
Baseline WHO clinical stage	Stage I/II	11	178	1		1	
	Stage III/IV	51	188	**3.948 [2.057, 7.577]**	**0.000**	**2.393 [1.228, 4.663]**	**0.010**
Past OI	Yes	27	142	1.063 [0.643, 1.759]	0.810		
	No	35	224	1			

Functional status	Working	49	298	1			
	Ambulatory	12	57	1.421 [0.755, 2.674]	0.276		
	Bed ridden	1	11	1.239 [0.171, 8.996]	0.832		
Tuberculosis	Yes	13	43	**2.036 [1.103, 3.756]**	**0.023**		
	No	49	323	1			
Initial NRTI backbone	AZT	40	56	**6.550 [3.885, 11.044]**	**0.000**	**8.188 [4.551, 14.732]**	**0.000**
	TDF	22	310	1		1	
Initial NNRTI	NVP	36	78	**3.503 [2.101, 5.840]**	**0.000**		
	EFV	26	288	1			
CPT prophylaxis	Yes	57	284	2.405 [0.961, 6.017]	0.061		
	No	5	82	1			
INH prophylaxis	Yes	27	208	0.634 [0.383, 1.050]	0.076		
	No	35	158	1			
Fluconazole	Yes	5	8	**3.343 [1.336, 8.369]**	**0.010**		
	No	57	358	1			
Co-medication	Yes	37	131	**2.260 [1.360, 3.755]**	**0.002**	**1.728 [1.034, 2.889]**	**0.037**
	No	25	235	1		1	
CD4 count	< 200 cell/mm3	27	143	1.105 [0.669, 1.826]	0.696		
	≥ 200 cell/mm3	35	223	1			
Baseline weight	<50 kg	27	158	1			
	≥ 50 kg	35	208	1.001 [0.605, 1.655]	0.391		
Baseline Hgb	< 7 g/gl	2	6	**3.397 [0.782, 14.754]**	**0.013**	**6.319 [1.397, 28.585]**	**0.017**
	7-9.9 g/dl	14	45	**2.279 [1.123, 4.626]**	**0.023**	**4.212 [1.924, 9.221]**	**0.000**
	10-12.9 g/dl	29	190	1.071 [0.589, 1.950]	0.822		
	≥ 13 g/dl	17	125	1		1	

*drivers, soldiers, custodians; HR= hazard ratio; CI=confidence interval; NRTI=nucleoside reverse transcriptase inhibitors; NNRTI=non-nucleoside reverse transcriptase inhibitors; OI=opportunistic infection; CPT= co-trimoxazole preventive therapy; INH=isoniazid; CD4 = cluster of differentiation; Hgb= hemoglobin

6. Discussions

Since the choices of regimen are still limited in most of low- and middle-income countries, well-managed first line cART is essential. Repeated investigation of the incidence of regimen modification and its determinants will help to keep patients on the first cART regimen as long as possible. Over the median follow-up time of 21 months (IQR 6 - 38), 62 (14.5%) of the patients in this cohort modified their initial antiretroviral regimen. This result is nearly in line with study conducted in Swaziland (15) but the proportion is somewhat lower than that reported from previous studies (29) and also studies in Ethiopia (25, 26). The probable reason for this may be explained as the previous studies had included stavudine in their first line regimen which may be the most common contributor for regimen modification due to drug toxicity but this study excluded stavudine due to its phase out during the study period.

The rate of initial regimen change among adult HIV patients on cART was found to be 7.66/100PY (95 % CI 5.84, 9.50 PY). This finding is lower than a study conducted in Swiss 41.5/100PY (27), Brazil 28.3/100PY (34), multicenter study in North America and Europe 14.4/100PY (35) and Thailand 13.8/100PY (28). This might be explained by the difference in defining outcome variables, since in this study treatment discontinuation was not considered as regimen modification unless they restart with different regimen. Furthermore, limited combined antiretroviral options or WHO based guideline in our setting may limit the clinician decision on cART modification due to treatment failure. The other possible reasons might be regular monitoring of viral load for treatment response in developed countries might pick virological failure earlier which calls the need for regimen change.

Similarly, it is lower than studies done in Kenya and West Africa with a rate of 18.6/100PY and 16.2/100PY respectively (33, 36). This might be due to the difference in follow up period 10.7 and 15 months in Kenyan and West Africa study but 21 months for our study. In addition to this, our study included participants who started cART after 2012 in which WHO recommended to phase out D4T but Kenyan and West Africa studies were done before 2011 which might overestimate the rate.

The main reason for regimen modification was toxicity which accounts about 45 (72.6%) of the cases and contribute for 5.56/100 PY (95% CI 3.98 - 7.14) followed by treatment failure 13 (21.0

%) and tuberculosis 4 (6.5 %). The common types of toxicities were anemia 23 (51.1%), rash 13 (28.9%), CNS toxicity 7 (15.5%), and renal failure 2 (4.4%). This is also similar with other studies (37) done in Mekelle (25, 26, 38) and Gondar (26).

In this study the baseline WHO clinical stage III/IV at initiation, co-medication with cART, AZT based initial NRTI backbone, and baseline hemoglobin of the patient was found to be predictors for initial regimen modification.

Those patients who were WHO clinical stage III/IV at the initiation of cART were 2.39 times at higher risk of changing their initial regimen as compared to those with WHO clinical stage I/II. This finding is also supported with studies done in Swaziland (15) and two Kenyan studies (33, 37) and study done in Gondar (26). This might be due to the fact that those patients who had advanced disease are likely to be on other medications which might result in drug interaction, side effect which in turns result in regimen modification.

Regarding the initial NRTI backbone, patients initiated with AZT based cART regimen had 8.19 times greater chance of changing their initial cART regimen compared to those initiated with TDF based cART regimen. AZT based regimen was the dominant regimen to cause initial cART regimen modification due to its hematological toxicity and this finding was harmonized with a number of different studies (39, 40). This result is also in agreement with study done in Mekelle (25). This might be justified possibly with those patients initiated with AZT based regimen were at the higher risk for developing hematological adverse effects and may result in regimen modification when compared with TDF based regimen as initial NRTI backbone.

Patients who were taking other concurrent medications with cART treatment were 1.73 times at a greater risk of changing their initial regimen at any time as compared to those who did not take other medication. This result shows that not to use additional drugs up on the cART regimen have a protective effect for treatment regimen modification. This study is also in line with Swiss HIV Cohort Study (27) and studies conducted in Ethiopia at Mekelle hospital (25) and Gondar Referral hospital (26). The possible reason for this may the need of co-medication particularly for comorbidities in patients with advanced disease and concomitant treatment of opportunistic infections, may cause drug-drug interactions, leading to an increase in transaminase levels and thus treatment modification as a result of drug-drug interactions and cumulative drug toxicity

which may finally leads to regimen modification. The other possible explanation might be poly pharmacy which could lead to poor adherence due to pill burden which in turn resulted in poor efficacy of treatment result in regimen modification secondary to treatment failure.

Patients having the low level of hemoglobin during the initiation of cART are at the increased risk for the modification of the regimen. Those patients with hemoglobin < 7g/dl were 6.32 times and those having between 7-9.9 g/dl were 4.21 times at increased risk of initial regimen modification. Even though this is not a significant predictor from previous studies, the reason might be explained as those patients with lower hemoglobin level were at higher risk of developing anemia which is one of the common reason for the treatment modification.

7. Strength of the study

This study was carried out in a routine clinical set-up, whose characteristics may represent the routine standard of care in most resource limited settings and thus allowing generalizability. Cohort study design since it is possible to see the temporal relationship between the risk factors since as the exposure precedes the outcome variable. As the sample size of this study is greater than the previous studies conducted in Ethiopia, this provided ample statistical power to assess factors associated with regimen modifications and it is more broadly generalizable to other settings. This is vital in informing clinicians on the time at which patients are at risk of modifying treatment and the possible factors that could influence modification at those time periods.

8. Limitation of the study

The finding of these study must be interpreted in light of its limitation. Because of the retrospective nature of the study, there are no detailed clinical information at the initiation of cART such as body mass index and viral load. Therefore, some of the important predictors of initial regimen modification which were significantly associated previously with initial regimen modification in studies done in other areas such as body mass index and hepatitis infection were missed. Various errors experienced with such a study design are likely to be present such as potential for risk of random misclassification error during recording by clinicians in that the biases may have influenced the results. On the other hand, it remains unclear whether there were additional clinical (e.g. drug-drug interactions or opportunistic infections), laboratory values (laboratory values associated with drug toxicities), or programmatic factors such as ARV supply chain considerations that were independent predictors of treatment modifications.

Another limitation is the possibility of potential informative censoring bias with patients who were either lost to follow up or dead. It is likely that the reasons leading to the loss to follow up or dead may have been related to the outcome of the study in that some of this patients might have been lost or died due to poor drug tolerability due to adverse events experienced or even treatment failure, and this could have the potential of under estimating the magnitude of cART modification. This limitation may also partially explain the very low treatment failure rate that was observed.

9. Conclusion and Recommendation

9.1 Conclusion

Initial regimen modification rate was found to be lower in this population than in cohorts in resource-settings and nearly half of the modification was occurred within the first six months of the initiation of cART. Being WHO stage III/IV at initiation, AZT based initial NRTI backbone, low baseline hemoglobin and co-medication with cART were found to be predictors of regimen modification. Therefore, special attention should be given for patients who are at advanced disease stage, AZT based regimen and taking additional medications other than cART. Toxicity was the most common reason for antiretroviral regimen modification as AZT was the most substituted drug with anemia being the most common side effect.

9.2 Recommendation

The findings of this study have several implications for the management of patients on treatment. The identification of toxicity as the main reason for cART modification calls for the need for early and proactive management of toxicity in order to prevent poor treatment outcomes including treatment failure to support patients in sustaining their first-line regimen for as long as possible. In addition, identifying the outcomes of patients lost to follow-up and how these may relate to the toxicities associated with cART, will be important next research question. The effect of these treatment modifications on the outcomes of patients in the future will need to be closely evaluated. Active programs for follow-up tracing should be adopted to access to detailed follow-up data to examine in order to understand the magnitude of this possible follow-up related bias. Increased treatment options, together with more frequent laboratory monitoring focusing on both possible toxicities and viral load will greatly assist clinicians and patients in making the best evidence-based clinical decisions possible. Thus, will be maximized the sustainability of first line cART regimens for HIV-infected patients in resource limited settings.

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11. Annexes

I. Data Abstraction tool

I. Socio demographic characteristics

ART Unique ID No. _____ Card No _____ _____

Date of initiation of ART_____ Months on ART_____

Current status of the patient _____

1. **Sex**
   - Male
   - Female
2. **Age** on initiation (years)_____
3. **Baseline weight**_____
4. **Marital status**
   - single
   - married
   - separated
   - divorced
   - widowed
5. **Educational status**
   - No formal education
   - Primary school education (1-8)
   - Secondary school education (9-12)
   - Higher institute education (Tertiary)
6. **Occupation**
   - Farmer
   - Daily labourer
   - Government employer
   - Merchant
   - Housewives

- Other (specify)_____

7. Religion

- Orthodox
- Protestant
- Catholic
- Muslim
- Others (specify)--------

8. Residence

- Urban
- Rural

9. Adherence

- Good
- Fair
- Poor

10. Disclosure

i. Disclosed

- Wife/husband
- Own child
- Parents
- Brothers/sisters
- Relatives
- Friend

ii. Not disclosed

II. Clinical, immunological characteristics and lab. Investigations

1. Weight (kg): At initiation of ART_____

1. Before ART switch_____
2. Latest weight _____

2. WHO clinical stage:

- During initiation of HAART _____

- Before HAART switch_____
- Latest WHO stage_____

3. Co-infections/comorbidity_____

4. Opportunistic infections

- Before HAART_____

5. Functional status

- Working
- Ambulatory
- Bed ridden

Base line CD4 count _____	Date _____
CD4 count before HAART switch _____	Date _____
Baseline Hgb _____	Date _____
Base line RFTs	Date _____
Base line LFTs	Date _____
Latest CD4 count _____	Date_____
Initial ART regimen_____	

III. Drug regimen modifications

Part 1: Patient changed ART regimen for the first time

Regimen switched to _____

Date of initial ART switch_____

Reason(s) for ART switch

Toxicity Anemia	Peripheral neuropathy	Lipodystrophy
Rash	Hepatotoxicity	Abdominal-pain

□ Nausea	□ Diarrhea	□ GI irritation
□ Headache	□ CNS toxicities	□ Fatigue
□ Amenorrhea	□ Renal failure	□ Dyslipidemia
□ Jaundice	Other toxicity (specify) _____	
Treatment failure □ Immunologic failure	Peak CD4_____	CD4 during change_____
□ Clinical failure	Clinical finding(s) _____	
□ Virologic failure	Baseline VL _____ VL during change _____	
□ **Pregnancy**	□ **Adherence difficulty**	□ **Stock out**
□ **Comorbidity**	Type of comorbidity _____	

Other reason (specify) _____

TB treatment

□ Yes

□ No

OI prophylaxis

□ Co-trimoxazole

□ Isoniazid

□ Fluconazole

Other Medications_____