Journal of
Virology Research and Advances in Vaccines

JScholar
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Research Article Open Access

Time to Initial Art Regimen Change of HIV Patients on Anti-Retroviral Therapy at Black Lion Hospital in Addis Ababa, Ethiopia

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Received Date: March 25, 2023 **Accepted Date:** April 24, 2023 **Published Date:** April 27, 2023

Citation: Fufa BG and Ayana GM (2023) Time to Initial Art Regimen Change of HIV Patients on Anti-Retroviral Therapy at Black Lion Hospital in Addis Ababa, Ethiopia. J Vir Res Adv Vac 2: 1-9.

Abstract

Background: Antiretroviral management brings a complex series of choices; when to initiate therapy, what regimen to use, which drugs within each class, when to change therapy, and which alternative drugs to use. Regimen change is a major challenge for the sustainability of human immunodeficiency virus (HIV) treatment program. Since the beginning of the epidemic, 75 million people have been infected with the HIV virus and about 32 million people have died of HIV. However, information on time to initial regimen scarce in Ethiopia.

Methods: The study was conducted at hospital in Addis Ababa, Ethiopia, from 2016 to 2019 amid adult HIV/AIDS patients. Analysis is depending on survival model, and it is fitting using survminer package of R software. Cox proportional hazard model is used to measure time to exit initial regimen. Model adequacy is checked using cox Snell residuals and marginal residuals. Model comparison is done using the AIC critreion.

Results: Out of 470, patients on the follow up 69 patients switch to second ART regimen with an incidence rate of 3.08/100 Person Year (PY). Having WHO clinical stage III at Initiation of ART regimen, occurrence of TB on Initial regimen were found to be predictors of Initial regimen. A unit decrease in CD4 count was associated with 0.9969 % increase hazard of switch to second line of ART regimen by keeping constant other variables in the model.

Conclusion: Risk rate of initial regimen change was found to be low and most of the change occurred within a year and half after initiation of HAART. Having WHO clinical stage III at Initiation of ART regimen, occurrence of TB on Initial regimen, decrease in CD4 count were found to be predictors of Initial regimen

Keywords: Initial Regimen Change, Cox Proportional Hazard Model, Adults, Art, HIV/AIDS

Abbreviations

AHR: Adjusted Hazard Ratio, AIC: Akakie Information Criteria, AIDS: Acquired Immune Deficiency Syndrome, ART: Anti-Retroviral Therapy, ARV: Anti-Retro Viral, BIC: Bayesian Information Criteria, BMI: Body Mass Index, CI: Confidence Interval, D4T: Stavudine, EFV: Efavirenz, FTC: Emtricitabine, HAART: Highly Active Anti-Retroviral Therapy, HIV: Human Immunodeficiency Virus, HR: Hazard Ratio, IPT: Interpersonal Therapy, KM: Kaplan Meier, NVP: Nevirapine, PHA: Proportional Hazard Assumptions, PY: Person-Years, RVI: Retroviral Infection, TB: Tuberculosis, TDF: Tenofovir Disoproxil Fumarate, WHO: World Health Organization, 3TC: Lamivudine

Introduction

The first cases of acquired immunodeficiency syndrome (AIDS) were reported in the United States in the spring of 1981. By 1983 the human immunodeficiency virus (HIV), the virus that causes AIDS, had been isolated and targets the immune system and weakens people's defense systems against infections and some types of cancers. As the virus makes disable and damage the function of immune cells, infected individuals gradually become immune deficient [1]. Since the beginning of the epidemic, 75 million people have been infected with the HIV virus and about 32 million people have died of HIV. Globally, 37.9 [32.7-44.0 million] people were living with HIV at the end of 2018. The WHO Africans region remains most severely affected, with nearly 1 in every 25 adults (3.9%) living with HIV and accounting for more than two-thirds of the people living with HIV worldwide. Ethiopia faces an epidemic among sub-populations and geographic areas, and in 2018, 690,000 peoples were living with HIV [2].

Antiretroviral management brings a complex series of choices; when to initiate therapy, what regimen to use, which drugs within each class, when to change therapy, and which alternative drugs to use. According to the Standard Treatment Guideline of Ethiopia; the criteria for initiating ART for adults and adolescents are; 1) if CD4 testing is available (a) WHO stage IV disease irrespective of CD4 cell count. (b) WHO stage III disease with CD4 cell counts below 350/mm3. 2) If CD4 testing unavailable; WHO stage III and IV disease irrespective of total lymphocyte count or WHO stage II diseases with a total lymphocyte count bellow 1200/mm3.

Regimen change is a major challenge for the sustainability of human immunodeficiency virus (HIV) treatment program. In a resource limited setting where treatment option limited designing strategy to increase the durability of original regimen are essential [3,4]. However, information on time to initial regimen change and its predictors is scarce in Ethiopia. Thus is the study we aimed time to initial regimen change of HIV patients at Black Lion Hospital, Addis Ababa, Ethiopia.

Methods

Study area

An institutional based backward looking follow up study was be in control of among adult HIV/AIDS patients in the middle of January 2016 and February 2019. The study was focused on ART clinic of Black Lion Hospital, Addis Ababa, which is the capital city of Ethiopia and the African union. it covered some selected positive HIV patients those who are adult age and on ART clinic follow up in study period. Black Lion Hospital has a thousands of adult HIV patients who are currently on ART.

Study population

The source population was all adult HIV/AIDS patients under ART, and all HIV/AIDS patients who enrolled between 2016 and 2019 at Black Lion hospital. However, subjects whose date of initial regimen change was unknown were excluded. The required sample for this study was obtained by using inclusion and exclusion criteria. From the total adult ART patients on the follow up at the specified time only those whose have minimum of two follow up were included, and as well as those who losts on follow up, drops, and etc were excluded from the sample.

Variables of the study

Survival end point were considered for the study; is the Initial ART regimen change during first January 2016 and first February 2019 and those patients doesn't switch to the second ART regimen between the specified time periods were considered as censoring values. Time to Initial ART regimen change in months was obtained subtracting date register to ART clinic from date of occurrence of event interest (Regimen change) where as for the censoring time was obtained by subtracting from the last visit of the HIV patients.

The predictor variables were: age, sex, marital status, educational status, and residence, Baseline CD4 count, history of TB, baseline functional status, baseline BMI, clinical stage, smoking, alcohol, and adherence at baseline.

Ethics approval and consent to participate

The ethical review committee of the College of Natural and Computational Sciences, Jimma University approved the study protocol. after, a support letter was obtained from the medical director of Black Lion hospital to get the medical cards of patients. Informed consent was not taken from patients enrolled in the study while the data was obtained from the patient's follow- up chart. Confidentiality during all time of research activities the data was kept on a secured system.

Data collection and quality

A uniform checklist was applied to obtain appropriate data by cheaking patient charts. Data for this study is secondary data routinely obtained from patients followed up at Black Lion public hospital. Health professionals who working at the hospital were nominated as data collector's and extracted by cheaking follow up chart and cards of patients. The health management information system (HMIS) card number was applied to diffirenciate individual patient cards. Then sociodemographic, baseline and follow up clinical as well as immunological data were collected from the date patient started to follow up until the end of the study.

Data analysis

The data entry was done using SPSS version 20 and then exported to R statistical software Version 4 for further analysis. Descriptive statistics were obtained and summarized using some tables, graphs, and texts. As well as Percentages, mean, and median were used to summarize for categorical variables and continuous variables. Median time to initial ART regimen change was estimated using the Kaplan-Meier (KM) method. The proportional hazard assumption was checked both graphically and using the Schoenfeld residual test for the survival model. The Cox proportional hazard was used as a measure of association for the survival model. Model adequacy was checked using cox Snell residuals and marginal residuals. Model comparison was done using AIC. Finally, the hazard ratio with a 95% confidence interval (CI) was computed and variables with P-value <0.05 in the multivariable analysis were taken as significant predictors for initial regimen change (5-10).

Results

Socio-demographic, Baseline Clinical and behavioral characteristics

The data consists of 470 HIV patients who were adult and on ART follow up between first January 2016 and first February 2019 in Black Lion Hospital. Among the total HIV patients 69 (14.68%) were switch their Initial ART regimen due to HIV whereas 401 (85.32%) were in Initial regimen. The estimated median age of those switch Initial regimen HIV patients were 39 years. The demographic information and some basic base line covariate from the HIV patients were observed by the categorical group of the covariates out of total of 470 HIV patients 196 (41.7%) of them were males and 32 (16%) switch the Initial ART regimen were also occurred in comparison with female HIV patient groups.

One hundred and three (21.9%) of the HIV patients belongs to WHO stage I groups, 201 (42.7%) belongs to WHO stage II groups while 129 (27.45%) belongs to WHO stage III groups, and 37 (7.8%) was belongs to WHO stage IV groups. From the total of HIV patients only 47 (10%) were smokers and of the total switch to second line occurred in smoking status category 17 (25%) of the switch to second line occurred in smoker category group when we made descriptive comparison with none smoker group (Table 1).

Table 1: Baseline socio-demographic, behavioural, clinical characteristics of patients on ART in Black Lion Hospital, Addis Ababa, Ethiopia

Variables	Frequency (%)
Sex	
Male	196 (41.7)
Female	274 (58.3)
Marital status	
Single	128 (27)
Married	230 (48.9)
Divorced	63(13.7)
Widowed	49 (10.4)
Educational status	
No-formal Education	31 (6.6)
Primary	110 (23.4)
Secondary	198 (42.1)
Tertiary	131 (27.8)
RVI-stage	
Stage **1**	103 (21.9)
Stage 2	201 (42.7)
Stage 3	129 (27.4)
Stage 4	37 **(7.887)**
Comorbidity	
No	438 (93.1)
Yes	32 (6.81)
Baseline functional status	
Working	390 (82.98)
Ambulatory	75 (15.9)
Bedridden	5 (1.06)
History of TB	
No	377 (80.1)
Yes	93 (19.79)
History of A DRs	
Poor	25 (5.3)
Fair	67 (14.26)
Good	378(80.43)
Alcohol status	
No	330 (70.21)
Yes	140 (29.79)
Smoking status	
No	423 (90)
Yes	47 (10)

Model diagnosis and Model comparisons

The proportional hazard assumption was checked by using the cumulative hazard plot and Schoenfeld residual test. For categorical covariates, we checked the proportional hazards assumption by appropriately transforming the Kaplan-Meier estimate. In this scale we would expect to see the parallel lines. Then, we observed the lines fitted the parallel line for both history of TB and usage of alcoholic are fulfill the proportional Hazard assumption. And for the continuous covariates, we tested the proportional hazards assumption using the Schoenfeld residuals. The output of the function reports a test for non-proportionality by using global test.

However, it is more useful to inspect the PH assumption by plotting the Schoenfeld residuals graphically. Then we observed that for baseline CD4 count randomly dispersed around 0 seems to hold PH assumption for the survival sub-model. (Figure 1, Figure 2).

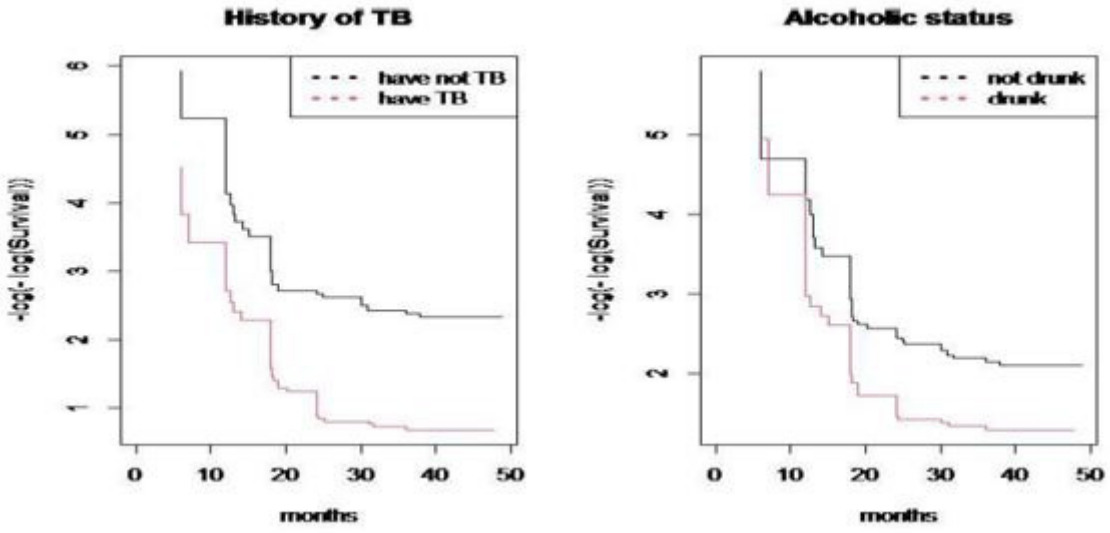

Figure 1: log-log plot for both history of TB and alcholic usage

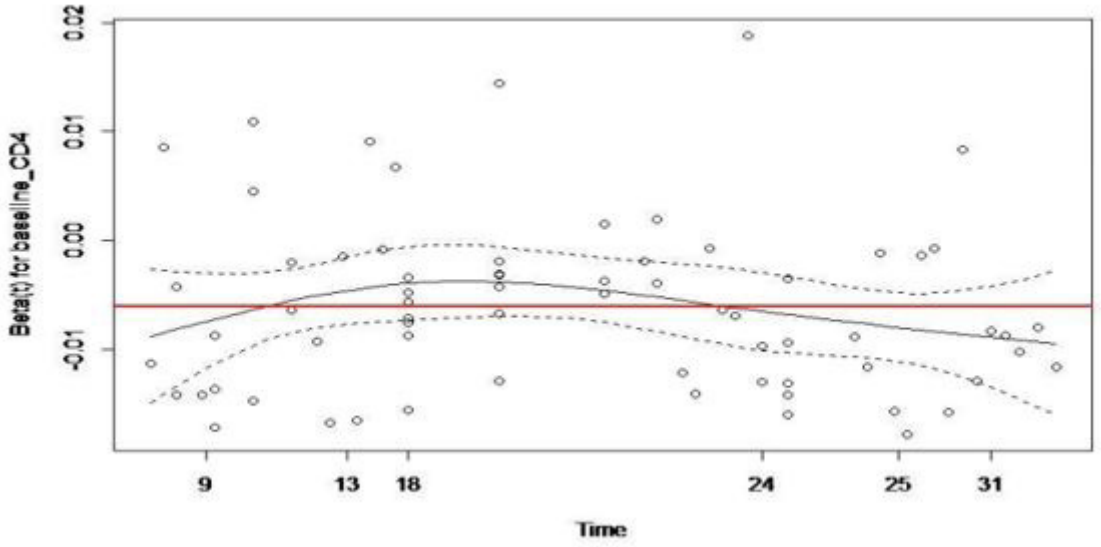

Figure 2: Schoenfeld individual test for CD4 count

Based on the assumption of the model with the lowest AIC and loglik ratio is the best-fitted model, the cox model was a parsimonious survival model.

Predictors of switch of ART regimen to second line

The hazards of switch to second ART regimen was 2.27 (95%CI [1.2704, 4.068]) times higher among patients who have TB history as compared to patients have no TB history. For patients with WHO I clinical stage baseline the hazard of experiencing switch to second line ART regimen is 0.96 times higher (95%CI [0.443, 2.118]) compared to WHO III clinical stage by keeping others stage constant, while a unit decrease in CD4 count was associated with 0.9969 % (0.994%, 0.999%) increase hazard of switch to second line of ART regimen by adjusting other variables in the model (Table 2). Then, WHO clinical stages, history of TB, and baseline CD4 count were the significant predictors to switch to second line of ART regimen.

Table 2: Cox survival of ART patients in Black Lion Hospital, Addis Ababa, Ethiopia

Fixed effects	Category	Betas	P-Value	95%CI
History of TB CD4	**NO**	1.0.92 -0.0031	<0.0001 <0.005	1 [0.23, 1.403] [-0.005, -0.001]
WHO clinical - stage(I)	Yes	-0.12	<0.00001	[-0.21, -0.03]

Discussion

This study was conducted to determine the predictor's of changing Initial ART regimen among adult HIV patients on ART at Black Loin hospital, Addis Ababa Ethiopia. Out of 470 followed up RVI patients 69, (14.71%) of them switch to second line of ART regimen with the incidence rate of 3.08 per 100 PY. This incidence of the current study was lower than that of a study done in Ethiopia at Gondar Referral Hospital with incidence density of 10.11 per 100-person [11]. Also this finding is lower than a study conducted in Thailand 13.8/100 PY [12], multicenter study in North America and Europe 14.4/100 PY, Brazil 28.3/100 PY [13]. This might be explained by the difference in defining outcomes variables, since in our case we didn't consider treatment discontinuation as regimen change unless they restart with different regimen. The other possible reasons might be regular monitoring of viral load for treatment response in developed countries pick virological failure earlier which calls the need for regimen change. In this study, being in WHO clinical stage three at initiation of ART, occurrence of TB on initial regimen, and CD4 count of the patients were found to be predictors of regimen change. According to the mentioned output, for patients with WHO III clinical stage baseline the hazard of experiencing switch to second line ART regimen is 0.96 times higher (95%CI [0.443, 2.118]) compared to other clinical stage by keeping others covariates constant, this finding is in line with studies done in Ethiopia, Gondar [11], Switzerland [14], Kenyan [15,16] which explained being in WHO clinical stage III at initiation of ART, occurrence of TB on initial regimen, co-medication with ART and side effect on initial regimen were found to be predictors of regimen change, and those who had started HAART at baseline WHO clinical stage III were nearly two times at higher risk of changing their initial regimen as compared to those with other WHO clinical stage. 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 drugs interaction, side effect which in turns result in drug change. The hazards of switch to second ART regimen was 2.27 (95%CI [1.2704, 4.068]) times higher among patients who have TB history as compared to patients have no TB history. This study is supported with the study done in Gondar [11], and India [12]. This says, patients those who had developed TB on initial regimen were nearly four times at higher risk of changing their initial regimen at any time as compared to those who didn't develop TB and another literature put it as one of the major reasons for regimen change [14,16,17]. In fact, tuberculosis is one of the opportunistic infection that occurs at any viral load level in HIV patient [15].

As it has the above strength, this study has its own

limitations. As the study was depend on secondary data collected from patient medical cards, important variables were not recorded which affected the initial regimen to change in the previous studies. As well as, since viral load measurement started recently we were not obtained repeatedly measured data that have the true effect on initial regimen to change.

Conclusion

Risk rate of initial regimen change is found to be low and most of the change occurred within a year and half after Initiation of HAART. Having WHO clinical stage III at Initiation of ART regimen, occurrence of TB on Initial regimen, decrease in CD4 count are found to be predictors of Initial regimen.

Consent to Publication

Not applicable

Competing Interests

There is no competing of interests related to this work

Authors Contributions

BGF selects the title, data curation, software, analyzed, and prepared the manuscript. GMA involved in conceptualization, design, interpreting findings, and prepared the manuscript. All authors read and approved the final manuscript.

Acknowledgments

First of all, we would like to forward our kindest regards to almighty God. We are greatfull to all participants in data collecton process. Finally, the authors would forward great thanks to the for the financial support to the first author.

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