

Competing Risk Model for Time to Development of Tuberculosis among Adults on Combination Antiretroviral Treatment

Lame Sharon Simon¹, Lesego Gabaitiri², Sikhulile Moyo^{3,4}, Kgalemelo Rodnie Mafa¹

¹Boitekanelo College, Gaborone, Botswana

²Botswana International University of Science and Technology, Palapye, Botswana

³Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

⁴School of Allied Health Professions, Faculty of Health Sciences, University of Botswana, Gaborone, Botswana

Email: lsimon@boitekanelo.ac.bw, kmafa@boitekanelo.ac.bw

How to cite this paper: Simon, L.S., Gabaitiri, L., Moyo, S. and Mafa, K.R. (2022) Competing Risk Model for Time to Development of Tuberculosis among Adults on Combination Antiretroviral Treatment. *Journal of Tuberculosis Research*, 10, 146-159. <https://doi.org/10.4236/jtr.2022.103011>

Received: April 12, 2022

Accepted: September 20, 2022

Published: September 23, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

The purpose of this study was to identify factors affecting the time to development of tuberculosis in the presence of competing risks. In this case death before developing tuberculosis was deemed a competing risk because it altered the occurrence of the outcome of interest being time to development of tuberculosis from baseline. We used data from a randomized longitudinal clinical trial study called the “Tshepo” study. The “Tshepo” study was a 3-year randomized clinical study following 650 ART-naïve adults (69.4% female) from Botswana who initiated first-line NNRTI-based ART. Participants were assigned in equal proportions (in an open-label, unblinded fashion) to one of 6 initial treatment arms and one of two adherence arms using permuted block randomization. Randomization was stratified by CD4+ cell count (less than 200 cells/mm³, 201 - 350 cells/mm³) and by whether the participants had an adherence assistant. Classical methods such as the Kaplan-Meier method and standard Cox proportional hazards regression were used to analyze survival data ignoring the competing event(s) which may have been inappropriate in the presence of competing risks. The idea was to use competing risk models to investigate how different treatment regimens affect the time to the development of TB and compare the results to those obtained using the classical survival analysis model which does not account for competing risks. Amongst 38 patients who died 15.8% of them developed tuberculosis whilst 84.2% of those who died did not develop the outcome of interest. The hazard ratio of treatment C was 1.069 implying that the risk of developing TB in patients taking treatment C is about 6.9% higher compared to those taking treatment A having adjusted for baseline age, baseline BMI, baseline

CD4, Hemoglobin and gender. Similarly, after accounting for competing risks the hazard ratio for treatment C was about 1.89 implying that the risk of developing TB amongst those taking treatment C was about 89% higher as compared to those taking treatment A. From the obtained results it was thus concluded that the standard Cox model of time to event data in the presence of competing risks underestimated the hazard ratios hence when dealing with data with multiple failure events it is important to account for competing events.

Keywords

Adults, Antiretroviral, Development, Risk, Tuberculosis

1. Introduction

Time to event data particularly in medical statistics is often complicated by the presence of competing events as they alter the occurrence of the outcome of interest. According to Gooley *et al.* [1], competing risks are events whose occurrence reduces the chance of the outcome of interest from occurring. An example of such multiple failure events data is when the event of interest was leukaemia amongst patients with the disease and death without relapse is deemed as a competing risk, Gooley *et al.* [1]. Another example could be where the event of interest is death due to prostate cancer with death from any other disease or event other than cancer being considered as a competing event. According to Gooley *et al.* [1], the methods of estimating the probability of failure for events which are subject to multiple failure events are not new and research has evolved in this area. Several researchers applied the complement of the Kaplan-Meier estimate (1 minus Kaplan-Meier) to represent the probability of occurrence of a specified endpoint even in the presence of competing risks. Gooley *et al.* [1] deemed the above approach as a misuse of the Kaplan-Meier estimate in the presence of competing risks. Thus, the classical approach such as the Kaplan-Meier estimate is not an appropriate measure when estimating the probability of failure in the presence of a competing event.

The Kaplan-Meier approach used to analyse time-to-event data in the presence of competing risks deemed any other event other than the outcome of interest as being censored, thus such events are removed from the risk set. The method overestimates the probability of the event of interest and yields misleading results in the presence of competing risks. According to Noordzij *et al.* [2], in the competing risk data, the assumption that an individual will experience the event of interest if the failure time is long enough is not viable, since the occurrence of the earlier competing event hinders the patient from experiencing the outcome of interest. The most appropriate method in competing risk analysis is the cumulative incidence competing risk (CICR) method which is based on the cumulative incidence function. This method considers all types of failure events.

Verduijin, [3] pointed out that the cumulative incidence which is defined as the probability of dying before time t , is made low by the occurrence of the competing events and patients experiencing the competing events are no longer at risk for developing the desired event of interest. The Classical method of analyzing time-to-event data such as the Kaplan-Meier estimate, overestimates the probability of failure in the presence of competing risks, hence the need for this study which considers the presence of competing risks. Competing events are crucial to any analysis of time-to-event data and cannot be ignored because their presence has an immense impact on the precision of estimates. The essence of this study was to compare the results of the two approaches of time to development of tuberculosis in the presence of competing events and adopt a reliable approach to model the survival time of time to development of tuberculosis.

Individuals who are HIV positive and enrolled on combinational antiretroviral therapy with a CD4 count of less than 350 cells/mm³ were more prone to opportunistic infections such as tuberculosis, pneumonia, and pulmonary tuberculosis. Amongst this cohort, there were several opportunistic infections such as pulmonary tuberculosis, herpes zoster, anemia, and any tuberculosis and Kaposi sarcoma. The prevalence of tuberculosis was high amongst this cohort as compared to other opportunistic infections with about 16.2% (105) amongst 650 patients enrolled on combinational antiretroviral therapy. Whilst the prevalence of Herpes zoster was 13.1% (85), that of Kaposi sarcoma was 1.4% (9), and the prevalence of pulmonary tuberculosis was about 13.1%. Hence it was of interest to study the most prevalent opportunistic infection amongst this cohort. Death was deemed a competing event since it hindered the observation of the event of interest and there were more mortality cases in this cohort with about 5.8% (38) reported cases of death.

1.1. Research Problem

The classical approach in survival analysis does not consider the presence of competing risks, rather they treat any other event other than the event of interest as being censored. Noordzij *et al.* [2] pointed out that competing risks hinders the observation of the event of interest or modifies the chance of developing the outcome of interest hence their accountability is trivial when doing analysis.

In Botswana, no study has looked at the incidence of tuberculosis in patients on combination antiretroviral therapy in the presence of competing risks hence the need for this research. Failure to account for competing risks could lead to insignificant conclusions when analyzing time to event data in the presence of competing risks and this is quite problematic. Hence such insignificant results when analyzing the relationship of treatments on time to the development of tuberculosis could yield incorrect results and a worse off treatment can be proved by the approach to be significant in increasing the survival time to the development of tuberculosis in the presence of competing risks when it in fact does not. Hence the need for such an approach so that correct treatment interventions could be decided to help increase the survival of HIV/AIDS patients who are suf-

fering from tuberculosis and perhaps come up with better treatment plans which could help reduce the risk of developing tuberculosis.

1.2. Research Focus

The focus of the study was to investigate the effect of covariates on the time to development of TB in the presence of competing risks. The study hopes to inform the “Tshepo” study on how competing risks can hinder or reduce the probability of the development of the outcome of interest and suggest to policy-makers and other researchers how the cumulative incidence competing risk method yields plausible results which are real-life probabilities of the failure time. The study is also relevant in medical institutions since better treatment interventions could be identified which would reduce the risk of developing tuberculosis amongst HIV/AIDS patients. Thus, the study could also suggest to policymakers which treatment combination works better in reducing the risk of developing tuberculosis amongst patients on combination antiretroviral therapy.

1.3. Research Aim and Research Questions

The objective of this study was to investigate factors associated with the time to development of pulmonary TB among adults living with HIV enrolled in combination antiretroviral therapy and how this relationship can be affected by competing risks factors. The study also compared cART regimens and how they affect the time to development of any tuberculosis among HIV infected adults.

The objectives were 1) to compare cART regimens: ZDV/3TC/NVP (Arm A), ZDV/3TC/EFV (Arm B), ZDV/ddI/NVP (Arm C), ZDV/ddI/EFV (Arm D), d4T/3TC/NVP (Arm E), and d4T/3TC/EFV (Arm F), using classical methods for survival analysis or methods that account for competing risks, 2) to identify other risk factors associated with time to development of any tuberculosis using standard methods for time-to-event, and 3) to analyze the relationship between covariates and development of pulmonary TB in the presence of competing risks.

2. Research Methodology

2.1. General Background

The secondary dataset used in this study was from the “Tshepo” study conducted by Botswana Harvard AIDS Institute Partnership. The study aimed at identifying risk factors for the development of tuberculosis on a cohort of 650 individuals who participated in the completed three year randomized antiretroviral treatment and drug resistance. The study design, study population, data collection and follow up were extracted from the study protocol that was prepared by the BHP study team.

The “Tshepo” study was an open label, randomized $3 \times 2 \times 2$ study conducted at Princess Marina Hospital in Gaborone, Botswana to evaluate the efficacy, tolerability, and development of drug resistance of six different first-line Cart re-

gimes: ZDV/3TC/NVP (Arm A), ZDV/3TC/EFV (Arm B), ZDV/ddl/NVP (Arm C), ZDV/ddl/EFV (Arm D), d4T/3TC/NVP (Arm E), and d4T/3TC/EFV (Arm F). This study also compared two different adherence strategies, standard of care (SOC) versus SOC plus community-based supervision (Com-DOT) to determine the optimal means of promoting adherence amongst adults receiving first line-Cart. Participants were assigned in equal proportions (in an open label, unblinded fashion) to one of 6 initial treatment arms and one of two adherence arms using permuted block randomization. Randomization was stratified by CD4+ cell count (less than 200 cells/mm³, 201 - 350 cells/mm³) and by whether the participants had an adherence assistant. Half of the participants were enrolled in each CD4+ cell count stratum, but there were no restrictions on whether they had an adherence assistant prior to study enrolment. The primary endpoints of the study were: the development of virologic failure with genotypic drug resistance and the development of treatment related toxicity, as defined by the first incidence of a grade 3 or higher adverse event. Secondary endpoints were death for any reason and time to non-adherence, as estimated by an adherence rate of less than 90%. ARV medication adherence was defined as being “excellent” (>90%) based on a composite measure of three types of data 1) patient four day and one month recall, 2) patient verbal reporting of the timing of doses, number of tablets per dose, and food requirements, and 3) ARV pill counts.

2.2. Sample

The sample consisted of adults (≥18 years of age), HIV-1 infected, cART-naïve Botswana citizens who attended one of the five ART screening clinics in Gaborone and were approached for possible enrolment. All potentially eligible adults had to qualify for cART based on existing Botswana national ARV treatment guidelines or having an AIDS defining illness or CD4 count ≤ 200/mm³ or meet the study’s eligibility criteria of a CD4+ cell count between 201 and 350 mm³ with a plasma HIV 1 RNA level greater than 55,000 copies/ml. Inclusion criteria were: haemoglobin value >8.0 grams/dL, absolute neutrophil count ≥1.0 × 10³/mm³, aminotransferase less than five times the upper limit of the normal, and for women of childbearing potential, a willingness to maintain active contraception throughout the duration of the study and a negative urine test within 14 days of study enrolment. Exclusion criteria were poor karnofsky performance score (40 or below), an AIDS-related malignancy other than mucocutaneous Kaposi’s sarcoma, grade 2 or higher peripheral neuropathy, major psychiatric illness and for women actively breastfeeding or less than six months post-partum.

2.3. Instrument and Procedures

Clinical and adherence assessments were done monthly at the study clinic. To monitor treatment efficacy, CD4+ cell counts, and plasma HIV-1 RNA levels were obtained at enrolment then every two months for the duration of the study. Laboratory safety monitoring included comprehensive chemistry and full blood count specimens at study enrolment then every month for the next six months

of the study, every two months during months 6 - 12 of study participation, and every four months during the remainder of the participation. In addition, all patients had lipid chemistries performed at baseline and then every six months.

Laboratory values were graded according to the 1994 Division of AIDS (DAIDS) laboratory grading scale.

2.4. Data Analysis

The risk set in time to event data analysis of all participants who are at the risk of developing the outcome of interest were deemed to be part of the risk set. At each point in time the risk set comprised of individuals who have not yet developed the outcome of interest during follow-up prior to the specific time point. In this approach, those individuals who experienced the event of interest and any other event other than the outcome of interest were removed from the risk set whilst in the competing event analysis those individuals who developed a competing event were kept in the risk set. Consequently, over time competing events form a greater proportion of the risk set prior to that time, their presence in calculations however was mitigated by weights, Sar-Pichhadze *et al.* (2016) [4]. In the non-parametric estimation, The Kaplan-Meier method estimates the probability of survival for a person from the time of origin to a given time point over Follow-up. In the competing risks approach, the probability of observing the outcome of interest is not identical for all participants without the desired outcome since competing events alter this probability of the event of interest whilst in the classical approach to survival analysis such competing events are thus censored. Thus, the Kaplan-Meier estimates fail to accurately estimate the probability of the outcome of interest hence competing risk approach which is deemed as robust in estimating the probability of the outcome of interest is adopted.

3. Research Results

The Performance of the proposed classical Cox proportional hazard model when failing to account for the presence of competing risks and the Cox proportional hazard model accounting for the competing risks were compared. Different variables were taken into consideration such as treatment arms, baseline age, baseline BMI, CD4 strata, hemoglobin, and gender. The comparison was done between the results of the two models.

Table 1 depicts the description of categorical variables by the outcome of interest being the development of tuberculosis. Amongst 109 patients taking treatment A about 15.6% of them developed tuberculosis whilst 84.4% of them did not develop tuberculosis. Similarly, amongst 109 of those taking treatment B, 20.2% of them developed tuberculosis and 79.8% of them did not develop tuberculosis. It can be concluded that the prevalence of tuberculosis is high amongst those taking treatment B with the prevalence of about 20.2% as compared to those taking the other treatments.

It is evident that of the 199 males enrolled in this study about 19.6% of them developed tuberculosis whilst amongst the 451 females about 14.6% of them developed tuberculosis. Amongst 38 patients who died 15.8% of them developed tuberculosis whilst 84.2% of those who died did not develop the outcome of interest. From the study the randomization was stratified by CD4 cell count thus those whose CD4 count was less than 200 cells/mm³. Amongst 330 patients whose CD4 count was less than 200 cells/mm³ 18.2% of them developed tuberculosis and 81.8% of them did not develop any tuberculosis. Similarly, for those whose CD4 cell count was between 201 - 350 cells/mm³ 14.1% of them developed tuberculosis and 85.9% of them did not develop tuberculosis (**Table 1**).

The above chart shows different treatment arms with the corresponding prevalence rates of tuberculosis. It is evident from above that, the prevalence of tuberculosis was higher for patients receiving treatment arm B as compared to all the other treatment arms. The second highest prevalence was from treatment arm C with the prevalence rate of about 16.7. Treatment arm D has prevalence of about 13.9% which means that it is a good treatment combination to reduce the risk of developing tuberculosis. Thus, treatment D can be suggested as a better treatment combination to be given to HIV/AIDS patients enrolled on combinational antiretroviral therapy to reduce the risk of developing tuberculosis (**Figure 1**).

Table 1. Prevalence of tuberculosis amongst different categorical variables.

Categorical Variables	Any TB		
	n	Yes (%)	No (%)
Treatment arm			
A	109	15.6	84.4
B	109	20.2	79.8
C	108	16.7	83.3
D	108	13.9	86.1
E	108	14.8	85.2
F	108	16.2	83.8
Gender			
Male	199	19.6	80.4
Female	451	14.6	85.4
Death			
Yes	38	15.8	84.2
No	612	16.2	83.8
Baseline CD4			
Less than 200 cells/mm ³	330	18.2	81.8
201 - 350 cells/mm ³	320	14.1	85.9

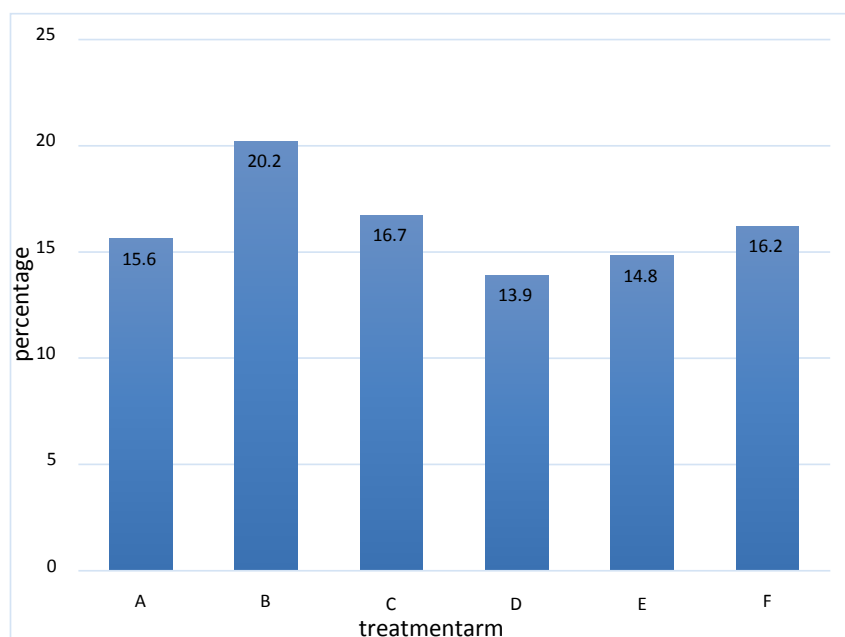


Figure 1. Prevalence of tuberculosis amongst different treatment arms.

Table 2 depicts different drug combinations administered to patients at the time of their entry into the study at their different follow up periods and different steps. From the analysis of different treatment arms and development of tuberculosis it is found out that the prevalence of tuberculosis was higher for those taking treatment arm B with 20.2% and was less on those taking treatment arm D with 13.9%. Hence, we can say that treatment arm B performs better than all the 5 treatment arms and should be recommended to patients enrolled on combinational antiretroviral therapy.

Table 3 Unadjusted Model: Hazard ratio comparing treatment B to treatment A was 1.059 implying that the risk of developing any TB is about 1.059 times higher for those taking treatment B compared to treatment A. The confidence interval for the above hazard ratio is (0.505, 2.223). Similarly, the hazard ratio of treatment C relative to treatment A is 1.096 depicting that the risk of developing any TB among patients taking treatment B is about 1.096 times higher as compared to those taking treatment A hence implying that treatment A performs better as compared to all treatments. Hazard ratio for baseline age is 1.036 implying that for every additional unit in age, the risk of developing any TB will increase by about 3.6%. Similarly for baseline BMI, a unit increase in the baseline BMI would decrease the risk of developing any TB by 4.6%. The hazard ratio for CD4 strata of 201 - 350 cells/mm³ is about 99.6% implying that the risk of developing tuberculosis is almost the same as for those with the CD4 cell count of less than 2000 cells/mm³. The hazard ratio for Hemoglobin is 0.973 which implies that for every unit increment in hemoglobin there is a corresponding decrease of the risk of developing any TB by about 2.7%. The hazard ratio of females is 0.0609 implying that the risk of developing any TB is about 93% less likely in females as compared to males.

Table 2. A table showing different treatment combinations administered in 3 steps.

TREATMENT ARM	STEP 1	STEP 2	STEP 3
Arm A	Zidovudine (ZDV), Lamivudine (3TC), and Nevirapine (NVP)	Didanosine (DDI), Stavudine (D4T),	
Arm B	Zidovudine (ZDV), Lamivudine (3TC), and Efavirenz (EFV)	and Nelfinavir (NEL)	
Arm C	Zidovudine (ZDV), Didanosine (DDI), and Nevirapine (NVP)	Stavudine (D4T), Lamivudine (3TC),	To be determined, according to Botswana National
Arm D	Zidovudine (ZDV), Didanosine (DDI), and Efavirenz (EFV)	and Nelfinavir (NEL)	ARV Treatment Guidelines
Arm E	Zidovudine (ZDV), Stavudine (D4T), and Nevirapine (NVP)	Didanosine (DDI), Zidovudine (ZDV),	
Arm F	Zidovudine (ZDV), Stavudine (D4T), and Efavirenz (EFV)	and Nelfinavir (NEL)	

Table 3. A table showing the classical Cox regression model.

VARIABLES	Unadjusted Model		Adjusted Model	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Treatments		0.998		0.991
ARM B	1.059 (0.505, 2.223)		0.991 (0.46, 2.120)	
ARM C	1.096 (0.507, 2.371)		1.069 (0.491, 2.325)	
ARM D	0.954 (0.433, 2.104)		1.008 (0.457, 2.223)	
ARM E	0.968 (0.455, 2.059)		0.884 (0.407, 1.918)	
ARM F	0.910 (0.421, 1.969)		0.826 (0.374, 1.24)	
ARM A	1			
BASELINE AGE	1.036 (1.009, 1.065)	0.010	1.034 (1.004, 1.066)	0.27
BASELINE BMI	0.954 (0.904, 1.007)	0.089	0.966 (0.912, 1.022)	0.226
CD4STRATA				
201 - 350 cells/mm ³	0.996 (0.635, 1.562)	0.985	0.911 (0.571, 1.453)	0.696
Less than 200 cells/mm ³	1			
HEMOGLOBIN	0.973 (0.855, 1.108)	0.680	0.907 (0.776, 1.060)	0.218
GENDER				
FEMALE	0.609 (0.385, 0.693)	0.034	0.552 (0.307, 0.994)	0.048
MALE	1			

Table 3 Adjusted Model: After adjusting for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender we found the hazard ratio for treatment B to be 0.991 implying that the risk of developing TB was about 1% lower for patients taking treatment B compared to those taking treatment A. The hazard ratio of treatment C is 1.069 implying that the risk of developing any TB in patients taking treatment C is about 6.9% higher compared to those taking treatment A having adjusted for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender. Similarly, the hazard ratio of treatment D was 1.008 depicting that those taking treatment D are about 0.8% more likely to develop any TB compared to those taking treatment A having adjusted for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender. The hazard ratio of patients taking treatment E is 0.884 implying that those taking treatment E are about 11.6% less likely to develop any TB compared to those taking treatment A adjusting for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender. Thus, taking treatment E is more effective in reducing the risk of developing any TB amongst patients enrolled on the combinational antiretroviral therapy treatment. After adjusting for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender we found the hazard ratio for treatment F is 0.826 implying that the risk of developing any TB amongst patients taking treatment F is about 17% less likely as compared to those taking treatment A adjusting for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender. After adjusting for treatment arms, baseline BMI, baseline CD4, Hemoglobin unit increment in age the risk of developing any TB amongst patients taking combinational antiretroviral therapy is about 3.4%. The hazard ratio for baseline BMI is 0.966 after controlling for treatment arms, baseline age, baseline CD4, Hemoglobin and gender which means that for every unit increase in the BMI of a patient enrolled in combination antiretroviral therapy the risk of developing any TB will decrease by about 3%.

After adjusting for baseline age, baseline BMI, treatment arms, Hemoglobin and gender were found the hazard ratio for CD4 strata of 201 - 350 cells/mm³ is 0.991 implying that the risk of developing TB is almost the same as for those with CD4 strata of less than 200 cells/mm³. The hazard ratio of hemoglobin was found to be 0.907 after adjusting for baseline age, baseline BMI, treatment arms, baseline CD4 and gender which implies that for every unit increase in hemoglobin the risk of developing any TB will reduce by about 9%. After adjusting for baseline age, baseline BMI, baseline CD4, treatment arms, and Hemoglobin the hazard ratio for females was 0.552 implying that females are about 45% less likely to develop any TB as compared to males. From the above model's treatment regimens B, C, D, E, F, were found to be statistically insignificant with the p-values being greater than 0.05 but we still have to include them into our final model since they are trivial to the analysis. Baseline age was found to be significant in the model with a p-value of 0.031 in our final model which is the adjusted model. Baseline BMI was found to be statistically insignificant in our final model hence was dropped. The variable baseline CD4 was similarly found to be

statistically insignificant in the adjusted model and hence was discarded in the final model. Hemoglobin was statistically insignificant and was dropped in the final model.

4. Discussion

The main objective of the study was to investigate factors associated with time to development of TB among HIV-infected adults enrolled in combination antiretroviral therapy and how this relationship can be affected by competing risks factors. We also compared cART regimens and how they affected time to development of any tuberculosis among adults living with HIV. Analyzing the effect of covariates on the outcome of interest which is tuberculosis it was found that, amongst 109 patients taking treatment A, about 15.6% of them developed tuberculosis whilst 84.4% of them did not develop tuberculosis. Similarly, amongst 109 of those taking treatment B, 20.2% of them developed tuberculosis and 79.8% of them did not develop tuberculosis. It can be concluded that the prevalence of tuberculosis is high amongst those taking treatment B as compared to those taking the other treatments. It is evident that of the 199 males enrolled in the study about 19.6% of them developed tuberculosis whilst amongst the 451 females about 14.6% of them developed tuberculosis. Amongst 38 patients who died 15.8% of them developed tuberculosis whilst 84.2% of those who died did not develop tuberculosis. From the study the randomization was stratified by CD4 cell count thus, those whose CD4 count was less than 200 cells/mm³ and those whose CD4 count was 201 - 350 cells/mm³. Amongst 330 patients whose CD4 count was less than 200 cells/mm³, 18.2% of them developed tuberculosis and 81.8% of them did not develop tuberculosis.

Similarly, for those whose CD4 cell count was between 201 - 350 cells/mm³ 14.1% of them developed tuberculosis and 85.9% of them did not develop tuberculosis.

When analyzing the risk of developing tuberculosis in the classical Cox proportional model the researchers found out that, for the unadjusted model, hazard ratio comparing treatment B to treatment A is 1.059 implying that the risk of developing any TB is about 1.59 times higher for those taking treatment B compared to treatment A. Thus, confidence interval for the above hazard ratio is (0.505, 2.223) and it contains one hence we can conclude that treatment A is better than treatment B. Similarly, the hazard ratio of treatment C relative to treatment A is 1.096 indicating that the risk of developing any TB among patients taking treatment C is about 1.096 times higher as compared to those taking treatment A hence implying that treatment A performs better as compared to all treatments. After adjusting for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender we found the hazard ratio for treatment B to be 0.991 implying that the risk of developing any TB is about 1% less for patients taking treatment B compared to those taking treatment A. The hazard ratio of treatment C is 1.069 implying that the risk of developing any TB in patients taking

treatment C is about 31% higher compared to those taking treatment A having adjusted for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender. Similarly, the hazard ratio of treatment D is 1.008 implying that those taking treatment D are about 8% more likely to develop any TB compared to those taking treatment A having adjusted for baseline age, baseline BMI, baseline CD4, Hemoglobin and gender.

In the competing risk model in **Table 4**, the risk of developing tuberculosis for adults on combination antiretroviral therapy is about 2.13 times higher for adults taking treatment B as compared to those taking treatment A. Thus, those taking treatment A are better. Similarly, the risk of developing tuberculosis amongst those taking treatment C is about 1.87 times higher as compared to those taking treatment A. Adjusting for baseline age, baseline BMI, Hemoglobin and gender the risk of developing tuberculosis amongst those taking treatment B was found to be 2.07 which implies that the risk of developing tuberculosis amongst those taking treatment B is about 2.07 times higher as compared to those taking treatment A when accounting for death as a competing risk. The classical Cox regression in the presence of competing risks underestimates the hazard ratios.

Table 4. Cox regression model in the presence of competing risks.

Variables	Univariate Model		Multivariate Model	
	Hazard ratio (95% CI)	P- value	Hazard ratio (95% CI)	P-value
Treatments		0.827		0.7073
Arm B	2.128 (0.532, 8.505)		2.07309 (-0.659, 8.3085)	
Arm C	1.869 (0.4471, 7.820)		1.9021 (0.4535, 7.9784)	
Arm D	2.473 (0.6392, 9.558)		2.6402 (0.6811, 10.233)	
Arm E	2.052 (0.513, 8.204)		1.7269 (0.4117, 7.2434)	
Arm F	1.705 (0.4074, 7.126)		1.776 (0.4236, 7.4528)	
Arm A	1			
Baseline Age	1.039 (0.997, 1.082)	0.064	0.99535 (0.991, 0.999)	0.03
Baseline BMI	1.0224 (0.948, 1.10)	0.56	1.0644 (0.987, 1.147)	0.1043
CD4 Strata				
201 - 350 cells/mm ³	0.667 (0.329, 1.350)	0.26	0.641 (0.325, 1.394)	0.2876
Less than 200 cells/mm ³	1			
Hemoglobin	0.751 (0.604, 0.931)	0.0091	0.6430 (0.504, 0.818)	0.00034
Gender				
Female	0.817 (0.394, 4.406)	0.59	0.70521 (0.330, 1.506)	0.37
Male	1			

5. Conclusions and Implications

It can be seen that on **Table 5** when accounting for death as a competing risk the hazard ratio comparing treatment B to A is about 2.15 which implies that the risks of developing tuberculosis amongst adults enrolled on combinational anti-retroviral therapy taking treatment B is about 2.15 times higher compared to those taking treatment A. Whilst under the classical Cox model the hazard ratio comparing those taking treatment B to A is about 1, thus we can then conclude that indeed the classical approach to competing risks underestimates the hazard ratios. It has been elaborated in the literature that analyzing time-to-event data in the presence of competing risks overestimates the probability of failure. According to Wolbers *et al.* [5], the use of Kaplan-Meier estimates for estimating the cumulative incidence function in the presence of competing risks is not ideal since subjects who experience the competing events would be treated as censored observations at the time of competing event occurrence, hence the estimator is deemed flawed in the presence of competing risks. For the ICD example the Kaplan-Meier “estimate” for the 5-year risk of having the first appropriate ICD therapy was 51% and the corresponding risk of death without prior ICD therapy was found to be 16%. Hence the latter is found to overestimate the correct CIF estimate of 10%. Hence for this apparent reason, the Kaplan-Meier estimate is not plausible in the presence of competing risks. Some have interpreted the Naive Kaplan-Meier estimate as corresponding to a world where the competing event is nonexistent. For instance, the 51% provided earlier would be interpreted as the risk of an appropriate ICD therapy as the method assumes that different competing risks are independent of each other, Wolbers *et al.* [4].

Table 5. Competing risk model and the classical Cox proportional model.

Variables	Competing risk model		Classical Cox proportional model	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-Value
Treatments		0.7784		0.999
Arm B	2.154 (0.537, 8.639)		1.001 (0.468, 2.140)	
Arm C	1.864 (0.445, 7.809)		1.068 (0.491, 2.332)	
Arm D	2.647 (0.683, 10.262)		1.010 (0.458, 2.228)	
Arm E	2.106 (0.526, 8.424)		0.886 (0.408, 1.923)	
Arm F	0.498 (0.393, 6.89)		0.831 (0.376, 1.834)	
Arm A	1			
Baseline Age	1.044 (1.000, 7.415)	0.045	1.033 (1.003, 1.064)	0.031
CD4 Strata				0.703
201 - 350 cells/mm ³	0.610 (0.298, 1.248)	0.176	0.915 (0.580, 1.444)	
Less than 200 cells/mm ³	1		1	
Gender				
Female	0.897 (0.425, 1.893)	0.045	1.816 (1.005, 3.283)	0.048
Male	1			

6. Recommendations

1) The study should be extended to cover the whole Botswana so that a vivid picture of the actual prevalence of tuberculosis and the actual risk of developing tuberculosis in the presence of death as a competing risk could be measured at a national level. 2) Local studies should adopt competing risks methods when dealing with time-to-event data which could be having multiple potential risks. 3) Policies should be formulated to come up with remedies to the TB epidemic in the country.

Acknowledgements

We express a heartfelt thanks to the Botswana Harvard AIDS Institute Partnership, the “Tshepo” Study Participants and Study Team for their immense contribution to the success of this work. We would like to express our deepest gratitude, sincere and grateful acknowledgement to Dr. Lesego. Gabaitiri and Dr Sikhulile Moyo for their meaningful suggestions and intellectual contributions and their guidelines throughout this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Gooley, T.A., Leisenring, W., Growly, J. and Storer, B.E. (1999) Estimation of Failure Probabilities in the Presence of Competing Risks: New Representations of Odd Estimators. *Statistics in Medicine*, **18**, 695-706. [https://doi.org/10.1002/\(SICI\)1097-0258\(19990330\)18:6<695::AID-SIM60>3.0.CO;2-O](https://doi.org/10.1002/(SICI)1097-0258(19990330)18:6<695::AID-SIM60>3.0.CO;2-O)
- [2] Noordzij, M.L.K. (2013) When Do We Need Competing Risk for Survival Analysis in Nephrology? *Nephrology Dialysis Transplantation*, **28**, 2670-2677. <https://doi.org/10.1093/ndt/gft355>
- [3] Verduijn, M., Grootendorst, D.C., Dekker, F.W., Jager, K.J. and le Cessie, S. (2011) The Analysis of Competing Events Like Cause Specific Mortality. *Nephrology Dialysis Transplantation*, **26**, 56-61. <https://doi.org/10.1093/ndt/gfq661>
- [4] Sapir-Pichhadze Pintilie, M., Tinkam, K.J., Loupacis Logan, A.G., Beyene, J. and Kim, S.J. (2016) Survival Analysis in the Presence of Competing Risks: The Example of Waitlisted Kidney Transplant Candidates. Wiley Periodical Inc. <https://doi.org/10.1111/ajt.13717>
- [5] Wolber, M., Koller, M.T., Stel, V.S., Schaer, B., Jagger, K.J., Leffonde, K. and Heinze, G. (2014) Competing Risks Analysis, Objectives and Approaches. *European Heart Journal*, **35**, 2936-2941. <https://doi.org/10.1093/eurheartj/ehu131>