JOINT MODELING OF LONGITUDINAL CD4 COUNT AND TIME-TO-DEATH OF HIV/TB CO-INFECTED PATIENTS: A CASE OF JIMMA UNIVERSITY SPECIALIZED HOSPITAL

By:

Aboma Temesgen

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Joint modeling of longitudinal CD4 count and time-to-death of HIV/TB co-infected patients: a case of Jimma University Specialized Hospital

MSc Thesis

By:

Aboma Temesgen

Advisor: Dr. Yehenew Getchew

Co-advisor: Mr. Abdisa Gurmesa

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JIMMA UNIVERSITY

SCHOOL OF GRADUATE STUDIES, DEPARTMENT OF STATISTICS

As thesis research advisors, we herby certify that we have read the thesis prepared by Aboma Temesgen under our guidance, which is entitled "Joint modeling of longitudinal CD4 count measurements and time-to-death of HIV/TB co-infected patients: a case of Jimma University Specialized Hospital", in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill University and Department style requirements; (2) its illustrative materials including tables and figures are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the University library.

Dr. Yehenew Getachew	_____	_____
Advisor	Signature	Date
Mr. Abdissa Gurmessa _	_____	_____
Co-advisor	Signature	Date

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Aboma Temesgen

Date: _____

Signature: _____

October, 2014

Jimma, Ethiopia

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ABSTRACT

Back ground: Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS; TB enhances HIV replication by accelerating the natural evolution of HIV infection which is the leading cause of sickness and death of peoples living with HIV/AIDS. Death is the serious problem that needs to be addressed so that maximum survival time can be obtained for the HIV/TB co-infection patients. Since the longitudinally measured CD4 count measurement is correlated with survival time joint modeling are used to handle the associations between these two processes to obtain valid and efficient survival time.

Objective: To indentify factors affecting change in CD4 count over time; risk factors for the survival time and associate change in CD4 count over time and time-to-death processes of HIV/TB co-infected patients.

Methods: The study consists of 254 HIV/TB co-infected patients who were 18 years old or older and who were on ART follow up from first February 2009 to fist July 2014 in Jimma University Specialized Hospital, West Ethiopia. First, data were analyzed using longitudinal and survival models separately. Then, based on the separate models several joint models with different random effects and different shared parameters have been explored and compared using deviance information criteria score.

Results: The median survival time was estimated 62.5 months. The linear mixed model showed functional status; weight and time effects have significant effect on the CD4 count measurement process; Cox and Weibull survival model showed base line weight; baseline smoking; separated marital status group and base line functional status have significant effect on hazard function of the survival time whereas the joint model showed subject specific base line value; subject specific linear and quadratic slopes of CD4 count process significantly affects the survival time of co-infected patient at 5% significance levels.

Conclusion: The longitudinally measured CD4 count measurement marker process is significantly associated with time to death and subject specific quadratic slope growth of CD4 count measurement; base line clinical stage IV and smoking is the high risk factors that lower the survival time of HIV/TB co-infected patients.

Key words: survival analysis; longitudinal analysis; Cox PH; linear mixed model; joint modeling; HIV-TB

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ACRONYMS

AIC	Akaike Information Criteria
AIDSCAP	AIDS Control and Prevention
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BIC	Bayesian Information Criteria
CI	Credible Interval (Bayesian) or confidence interval (classical)
CMD	Common Mental Disorder
DF	Degree of Freedom
DIC	Deviance Information Criteria
DOTS	Direct Observed Treatment Short course
FMOH	Federal Ministry of Health
FMOHE	Federal ministry of Health Ethiopia
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
JUSH	Jimma University Specialized Hospital
LMM	Linear Mixed Effects Models
LOWESS	Locally Weighted Smoothing of Scatter plots.
MCMC	Markov Chain Monte Carlo
ML	Maximum Likelihood
MOH	Ministry of Health
MOHE	Ministry of Health Ethiopia
NPMLE	Nonparametric Maximum Likelihood Estimators
PSA	Patient Specific Antigen
PLWHA	People Living with HIV/AIDS
TB	Tuberculosis
UNAIDS	United Nations Program of HIV/AIDS
WHO	World Health Organization

1. INTRODUCTION

1.1. Back ground and relations ships between HIV and TB infections

Tuberculosis is a bacterial disease caused by micro bacterium tuberculosis (tubercle bacilli) which is the leading cause of death among people infected with HIV. Whereas the transmission of TB occurs by airborne spread of infectious droplets when sharing common closed environment with TB infected individuals (WHO, 2006)

HIV, the Human Immunodeficiency Virus, is the etiological agent responsible for the acquired immunodeficiency syndrome (AIDS). There are multiple modes of HIV transmission including sexual intercourse, sharing needles with HIV-infected persons, or via HIV-contaminated blood transfusions. Infants may acquire HIV at delivery (birth) or through breast feeding if the mother is HIV positive. HIV severely weakens the immune system. Hence, it makes people highly vulnerable to invasions by a great number of infectious agents including mycobacterium, the etiological agent responsible for TB. There is a long latent period associated with HIV infection and the onset of HIV-related diseases including AIDS in adults. As HIV infection progresses, immunity declines and patients tend to become more susceptible to "common" or even rare infections (WHO, 2009).

Close to one third of the world's population living with dormant or latent TB can develop active TB when their immune systems are compromised (be it through general poor health or through another infection, like HIV) active TB can develop and without treatment will most certainly be fatal. HIV-negative person with a latent TB infection has a 10% chance of progressing to active TB over his or her entire lifetime, whereas HIV-positive person has a 10% chance of developing active TB each year (Stop TB, 2006).

TB is the leading cause of death among HIV infected people; the WHO estimates that TB accounts for up to a third of AIDS deaths worldwide. When individuals are infected with TB, the likelihood of them becoming sick with the disease is increased many times if they are also HIV positive and people with latent TB are increasingly becoming infected with HIV and many more are developing active TB because HIV is weakening their immune system. People who are co-infected with both HIV and latent TB have an up to 800 times greater risk of developing active TB disease and becoming infectious compared to people not infected with HIV (USAID, 2014).

1.2. Global burdens of HIV/TB co-infections

Globally the number of TB patients who had been diagnosed with HIV status reached 2.1 million in 2010, equivalent to 34% of notified cases of TB. Of the 8.8 million incident cases globally an estimated 1.1 million (13%) were found to be co-infected with HIV (WHO, 2012). Overall, the African region accounted for a staggering 82% of all new TB cases co-infected with HIV. Among the TB patients 46 % of them are those living with HIV globally and 42% TB patients in the African region were living with HIV in 2010. Among the PLWHA enrolled in HIV care worldwide in 2010 the treatment success and death rates reported for HIV positive TB cases in 2009 were 72% and 20% respectively(WHO,2012).

In many societies HIV and TB treatments are common today and the use of drugs has altered the joint dynamics of TB and HIV. About one third of 39.5 million HIV-infected people worldwide are co-infected with TB (WHO, 2006) and up to 50 percent of individuals living with HIV are expected to develop TB. Many TB carriers who are infected with HIV are 30 to 50 times more likely to develop active TB than those without HIV (Sharma *et al,* 2005). The HIV epidemic has significantly impacted the dynamics of TB. In fact, one-third of the observed increases in active TB cases over the last five years can be attributed to the HIV epidemic. For individuals infected with HIV, the presence of other infections, including TB tends to increase the rate of HIV replication. This acceleration may result in higher levels of infection and rapid HIV progression to the AIDS stage (Sharma *et al,* 2005).

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS and TB is the most common infectious disease affecting HIV-sero positive individuals and causing to their death(AIDSCAP, 2000; Raviglione *et al.,* 2005). HIV infection has contributed to a significant increase incidence of TB worldwide by producing a progressive decline in cell-mediated immunity. HIV also alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV co-infected individuals and leading to more frequent extra pulmonary involvement, atypical radiographic manifestations, and paucity bacillary disease, which can impede timely diagnosis. Although HIV related TB is both treatable and preventable, incidence continues to climb in developing nations wherein HIV infection and TB are endemic and resources are limited (AIDSCAP, 2000; Raviglione *et al.*, 2002).

1.3. Burdens of HIV/TB co-infections in Sub-Saharan Africa

Sub-Saharan Africa has borne the burden of HIV/TB co-epidemic. Over the past 20 years, HIV has fuelled TB notification rates, which have increased 3- to 5-fold in many African countries. By 2007, the continent accounted for 79% of the global burden of HIV-associated TB (WHO, 2009). Worst affected are those countries in the east and south of the continent where HIV prevalence rates are highest. In South Africa and Swaziland, approximately 1% of the population develops TB annually. Notification rates in some poor communities in South Africa have even increased to over 2% per year rates that are almost unprecedented in the era of short-course multi-drug chemotherapy (Lawn *et al.* (2006), Middelkoop *et al.* (2008)).

HIV infection is now the most common predictor of TB incidence and the other way round, TB is a common infection in sub-Saharan Africa. Thus, these countries continue taking the leading position in HIV/TB morbidity and mortality rate, where the TB epidemic is primarily driven by HIV infection. Ethiopia is one among these countries most heavily affected by HIV and TB co-infection. The world health organization ranked Ethiopia as 7th among the 22 high burden countries with TB in estimated annual incidence of 379 cases and prevalence of 643 cases per 100,000 populations (WHO, 2008) and the prevalence of HIV among TB patients is up to 41% (Demissie et al. 200,Yassin *et al.*, 2004).

1.4. Burdens of HIV and TB co-infections in Ethiopia

The incidence of TB in Ethiopia is estimated to be 379 per 100,000 populations for all cases and the prevalence 643 per 100,000 populations (WHO, 2008). According to data from the Ministry of Health, TB is the leading cause of morbidity, the third cause of hospital admission and the second cause of death in Ethiopia (FMOHE, 2009). Ethiopia is also one of the country worst affected by the HIV epidemic, with a total of 1.2 million people living with HIV in 2007 (FMOHE, 2007).

HIV infection is a major public health problem in Ethiopia. Prior to 1985, HIV prevalence was very low in the country, but has increased rapidly in the years following. The adult HIV prevalence in the country was 0% in 1984, 1.0% in 1989, and 3.2% in 1993. HIV infection has now spread throughout the country and AIDS cases have been reported from every region of the country. By 1997, the adult prevalence had increased to 7.4% and about 2.4 million HIV infected

adults live in Ethiopia today. In the urban areas, the HIV prevalence is much higher (21%) compared with the rural areas 4.5% (MOHE, 2006)

In Ethiopia, the number of TB cases has also been rising rapidly (MOHE, 2005). The number of reported new cases has increased from 55,000 to 100,000 in the last ten years. TB is among the leading causes of morbidity, hospital admission and the first cause of hospital deaths (J. Lim *et al.*, 2013) this increase in the number of tuberculosis cases is in part thought to be due to the rapid spread of the HIV infection. Except for very few hospital-based studies conducted in different parts of the country, there is no adequate information on the prevalence of TB/HIV co-infection in the country. The aim of this study was to determine the prevalence of HIV infection in a representative sample of sputum positive tuberculosis patients in Addis Ababa.

In Ethiopia routine data from 44 sites in the year 2005/6 showed 41% of TB patients were HIV positive. In addition, another routine data collected in 2006/07 estimates that 31% of TB patients are HIV positive (FMOHE, 2008). TB was the cause of 76 thousands deaths in Ethiopia, out of which 30% were among HIV positive patients. However, WHO recommends different collaborative activities for HIV/TB co-infections where one is initiation of antiretroviral therapy. Antiretroviral therapy (ART) is an essential treatment for HIV infection in order to reduce the risks of death and HIV-related morbidities, or in improvement of quality of PLWHIV (WHO, 2009).

1.5. Joint modeling approaches

In recent years, the interest in longitudinal data analysis has grown rapidly through the development of new methods and the increase in computational power to aid and further develop this field of research. One such method is the joint modeling of longitudinal and survival data.

It is commonly found in the collection of medical longitudinal data that both repeated measures and time-to-event data are collected. These processes are typically correlated, where both types of data are associated through unobserved random effects. Due to this association, joint models were developed to enable a more accurate method to model both processes simultaneously. When these processes are correlated, the use of independent models can cause biased estimates (Little,2002; Ratclie *et al*.,2004;Yi-Kuan Tseng ,2005), with joint models resulting in a reduction in the standard error of estimates. Thus, with more accurate parameter estimates, valid inferences concerning the effect of covariates on the longitudinal and survival processes can be obtained.

A common objective in longitudinal studies is to characterize the relationship between a longitudinal response process and a time-to-event. Considerable recent interest has focused on so-called joint models, where models for the event time distribution and longitudinal data are taken to depend on a common set of latent random effects. In the literature, precise statement of the underlying assumptions typically made for these models has been rare (Tsiatis and Davidian, 2012).

Longitudinal studies often produce two types of outcome, namely a set of longitudinal response measurements and the time-to-event of interest, such as death, development of a disease or dropout from the study. Two typical examples of this setting are HIV and cancer studies. In HIV studies patients who have been infected are monitored until they develop AIDS or die, and they are regularly measured for the condition of the immune system using markers such as the CD4 lymphocyte count or the estimated viral load. Similarly in cancer studies the event outcome is the death or metastasis and patients also provide longitudinal measurements of antibody levels or of other markers of carcinogenesis, such as the PSA levels for prostate cancer. These two outcomes are often separately analyzed using a mixed effects model for the longitudinal outcome and a survival model for the event outcome. However, in mainly two settings a joint modeling approach is required. First, when interest is on the event outcome and we wish to account for the effect of the longitudinal outcome as a time-dependent covariate, traditional approaches for analyzing time-to-event data (such as the partial likelihood for the Cox proportional hazards models) are not applicable(Rizopoulos ,2010).

Joint modeling enables the simultaneous study of a longitudinal marker and a correlated time-to-event. Among them, the shared random-effect models that define a mixed model for the longitudinal marker and a survival model for the time-to-event including characteristics of the mixed model as covariates received the main interest. Indeed, they extend naturally the survival model with time-dependent covariates and offer a flexible framework to explore the link between a longitudinal biomarker and a risk of event (J.D. Tapsoba, 2009).

A popular approach in modeling survival time and longitudinal data measured with error consists in modeling simultaneously both the time-to-event data and the covariate process. This makes possible the exploitation of the information contained in both data in dealing with the measurement errors. Joint modeling often assumes a proportional hazards model for the survival

times and a linear mixed-effects model for the longitudinal data. Under this framework, different approaches have been proposed in the literature including some likelihood based methods with an assumption on the distribution of the random effects and that of the measurement errors (Wulfsohn M. *et al*,1997).

Tsiatis *et al*. (1995) proposed a two-stage approach in which, based on an approximation to the hazard function for the event times, the usual partial likelihood for the Cox model can be used. In this approach the observed covariate history is estimated using empirical Bayees methodology, which requires fitting as many mixed effects models as there are event times in the data set.

The approach that this study used to build a joint model is simultaneously modeling the longitudinal CD4 measurements and the time-to-death processes by linking those using shared random effects parameter model. In the proposed model, to characterize the longitudinal CD4 measurements a linear mixed effects model that incorporates patient specific CD4 intercept and slopes is used for the longitudinal sub-model while Cox PH model is used to describe the time-to-death survival data for the survival sub-model. Then, the two sub-models are linked through shared parameters (Wu, 2010), with different forms, since these random effects characterize the subject specific longitudinal process. Because, the standard maximum likelihood method involves integrating out the shared parameters from the log-likelihood function which is difficult when dealing with high dimensional variables (Xin et al, 2009), a Bayesian estimation procedure and a Markov chain Monte Carlo (MCMC) algorithm is used to fit the joint model. At last, the convergence of the Gibbs sampler is monitored by examining time series plots of the parameters over iteration.

The thesis is organized as follows: The statement of problem and objectives of the study are presented next in this section. Section 2 describes some literatures related HIV/TB co-infection and different joint modeling approaches. In Section 3, the data and the detail methods of data analyses employed are explained. Then, basic results of the study are presented in Section 4 and discussed in Section 5. Finally, some concluding remarks and recommendations are provided in Section 6.

1.6. Statement of the problem

Generally it is recommended that HIV infected patients start to take ART in order to reduce AIDS related mortality and morbidity, or to improve their quality of life. But, in most cases TB co-infection violates and disturbs this issue. Moreover, death during TB treatment and shortened life are recognized in HIV/TB co-infected patients. To overcome this problems of HIV/TB co-infection many well established methods exist for analyzing longitudinal and survival of HIV/TB co- infection data separately; including linear mixed effects models for longitudinal modeling part, and semi parametric or parametric models for survival modeling part. But their separate use may be inappropriate since the longitudinal measured CD4 count process is correlated with patient health status, hence the survival endpoint, as well as the possibility of study survival.

Joint modeling of longitudinal and survival data, on the other hand, incorporate all information simultaneously and provide valid and efficient inferences. But, by separate modeling, the interrelationships of the two responses cannot be well investigated. For example, the CD4 cell counts are measured at different times for each co-infected patients, hence, the CD4 level changes from time to time for each patient and this change in CD4 level over time of the co-infected patient related to the patient health status the separate modeling would not able to examine the effect of these differences of the longitudinal response on the survival outcome but joint modeling does. The main aim of this study was to associate survival time from co-infection to death and characteristics of the longitudinal CD4 count measurements trajectories such as patient-specific slopes or intercepts. In general, the study addresses the following major research questions:

1. Which shared parameter association structure is an appropriate in the joint modeling of longitudinally measured CD4 count processes and time to death of HIV/TB co-infected patients to indentify how unobserved longitudinally measured CD4 count to survival time of HIV/TB co-infected patient?

2. Is the rate of change of CD4 measurements from one time to another is the risk factor for the survival times of co-infected patient?
3. Which appropriate longitudinal and survival separate models is an appropriate for the joint modeling to associate longitudinal CD4 marker with survival time of co-infected patients?
4. Which covariate is highly the risk factor for the survival of the HIV/ TB co-infected patients?

To answer these research questions and also to identify the different covariates related to survival of the co- infected patients, the main aim of the study was on modeling of the survival model; the longitudinal model finally joint modeling using shared parameters that associated the two processes properly. The focus was given for joint modeling of the longitudinally measured CD4 count marker and time-to-death of HIV/TB co-infection patients' in order to know the contribution of longitudinally measured CD4 counts on the survival time of the co-infected patient by giving focus on the two processes.

1.7. Significance of the study

The results of this study will be useful for the TB/ HIV co-infected patients by identifying the risk factors for their survival time. It also helps the health sectors as inputs to create awareness for the community on the risks for the survival of TB/ HIV co-infection. It also used an input for researchers who want to investigate on HIV/TB co-infection related areas by pointing directions to be addressed in the future. It also helps the clinicians to give consultancy and awareness for their co-infected patients depending on the identified risk factors

1.8. Objectives

General objective

The main objective of the study was joint modeling of both the longitudinal CD4 measurements and time-to-death of HIV/TB co-infected patients using shared parameters.

Specific objectives

Specifically the study addresses the following specific objectives:

- explores an appropriate linear mixed model for the CD4 counts over time that predicts the evolution of CD4 since it is the marker for HIV/TB co-infection.
- explore an appropriate survival model which appropriately predicts the survival time and relate the risk factors for the HIV/ TB co-infected patients.
- determines an appropriate association structure that appropriately associate between longitudinally measured CD4 count process and time-to-death of HIV and TB co-infected patients process for the joint modeling to know the association between the two processes
- determine the risk factors associated with the survival of HIV/TB co-infected patients.

2. LITERATURE REVIEW

2.1. General reviews on HIV/TB co-infections

USAID (2014) on its fact sheet publications noted that HIV/AIDS and TB co-infection present special challenges to the expansion and effectiveness of DOTS programs and the Stop TB Strategy. TB accounts for one-quarter of AIDS deaths worldwide and is one of the most common causes of morbidity in people living with HIV and AIDS (PLWHA). Currently, approximately 34 million people are infected with HIV, and at least one-third of them are also infected with TB. The dual epidemics of TB and HIV are particularly pervasive in Africa, where HIV has been the most important contributing factor in the increasing incidence of TB over the last 10 years. In some countries in sub-Saharan Africa, up to 80 percent of individuals with active TB disease are also HIV-positive. The dual epidemics are also of growing concern in Asia, where two-thirds of TB-infected people live and where TB now accounts for 40 percent of AIDS deaths.

Study conducted on Human immunodeficiency virus (HIV) infection in tuberculosis patients in Addis Ababa by Demissie *et al.*(2000) with objective of to determine the prevalence of HIV infection in a representative sample of sputum-positive tuberculosis patients showed that of the 236 blood samples collected, 107(45.3%) were HIV positive. Among the HIV positives, 66 (61.7%) were male and 41(38.3%) females. The HIV-TB co-infection was highest in the age group 20-49 and the largest number of TB co-infection (75% of all such co-infection) was found in the 20-39 age groups. There was no significant difference between the HIV positive and negative TB patients concerning to other socio-demographic factors or presenting symptoms.

Abera *et al.* (2006) conducted an ecological study on the association between HIV and TB in Oromia regional state, Ethiopia in 2006/7 with the main objective of assessment of association between infection with HIV and tuberculosis of the total of 40779 cases of TB including 12818 smear positive pulmonary TB cases and 29,590 positive for HIV infection and found that the prevalence of HIV infection was significantly associated with the incidence of TB in Oromia region. The ecological association between different types of tuberculosis and prevalence of HIV across zones and towns in Oromia was estimated using the Spearman's correlation. The study has also shown that similar associations were also seen between prevalence of HIV infection and the incidence of smear positive tuberculosis, smear negative tuberculosis and extra-pulmonary tuberculosis.

Cross sectional study done by Deribew *et al.* (2010) on three Oromia regional state hospitals (Adama, Nekemte and Jimma), Ethiopia from February to April,2009 with the main objective of investigating the relationship between TB/HIV co-infection and common mental disorders (CMD) consisting of 155 TB/HIV co-infected and 465 non-co-infected HIV patients and results of the study obtained by using logistic regression showed that TB/HIV co-infected patients had significantly (p value- 0.001) greater risk of CMD (63.7%) than the none co-infected patients (46.7%) [OR = 1.7, (95%CI: 1.0, 2.9)].

Mohammed *et al.* (2011) conducted a case control study in Jimma and Mettu Karl Hospitals where the two hospitals serve as referral and treatment centers for HIV and TB in south-west Ethiopia from January to March, 2009. The study population consisted of 162 cases and 647 controls. Cases were adult people living with HIV/AIDS who developed active pulmonary tuberculosis and controls were people living with HIV/AIDS without active tuberculosis. The objective of the study is to identify the risk factors of active pulmonary TB among PLWHIV using multiple logistic regression models. The final multivariate model was obtained by a forward and backward variables selection procedure. Then, the result reveals that, after adjustment for potential confounders, an initial weight less than 18.5 kg [OR=4.1 (95% CI: 2.3, 7.4), a CD4 lymphocyte count less than 200 cells/mm^3 [OR=9.8(95% CI: 5.5, 17.5)], WHO clinical stage IV (OR=4.3; 95% CI: 2.6, 6.8) and not taking antiretroviral treatment [OR=3.1(95%CI: 1.9,4.9)] were independently associated with the development of active tuberculosis in people living with HIV/AIDS.

Unmatched case-control study was conducted from December 26, 2011, to February 29, 2012 with 123 TB infected HIV positives cases, and 246 non-TB infected HIV positives control by Hatoluf Melkamu *et al.* (2013) with the main objective assessment of determinants of TB/HIV co-infection among adult HIV positives attending clinical care at two public health facilities in Nekemte, western Ethiopia. They found Being divorced/widowed AOR = 3.02, 95% CI (1.70, 7.88), not attending formal education [AOR = 4.32 (95% CI:2.20, 14.15)], being underweight (BMI < 18.5 kg/m2) AOR = 3.87, 95% CI (2.18, 6.87), having history of diabetic mellitus [AOR = 3.63, (95% CI ;1.33,9.94], and being in advanced WHO HIV/AIDS clinical staging [AOR = 2.29,(95% CI :1.32, 3.98)], were determinant factors associated with TB/HIV co-infection. Having a separate kitchen [AOR = 0.48, (95% CI: 0.28, 0.81)] showed protective role.

observational, analytic, case-control and quantitative study by Obsa (2013) on his thesis of risk factors associated with HIV co-infection in HIV/AIDS patients taking antiretroviral therapy (ART) in one of the public health facilities in Ethiopia with main objectives of assessment of risk factors associated with TB co-infection in HIV/AIDS patients taking antiretroviral therapy (ART) with randomly selected 367 HIV and AIDS patients of whom 92 of them were TB co-infected and found educational status, waste disposal system, monthly income, contact history with a patient of active tuberculosis or presence of a family member with active tuberculosis, drug adherence, knowledge on tuberculosis prevention and history of exposure to substance were factors independently associated with the occurrence of active tuberculosis among HIV and AIDS patients taking ART. The study also heighted the need for on-going educational, informational and other interventions to address the risk factors of tuberculosis in HIV and AIDS patients in order to decrease the rate of TB co-infection.

Tadesse *et al.* (2013) conducted study on HIV co-infection among tuberculosis patients in Dabat, northwest Ethiopia with main objective to determine the prevalence of HIV co-infection among TB patients in Dabat district, northwest Ethiopia using records of 1086 pulmonary and extra pulmonary tuberculosis patients registered from 2009 to 2012 at two health centers in the district. The study found that the prevalence of HIV co-infection 97 (11.4%), the majority, 61 (62.9%) and 90 (92.8%) of them were females and belonged to socio-economically productive age group, respectively. About half, 48 (49.5%) were smear-negative pulmonary tuberculosis patients. The study also concluded call for an emergency reaction through strengthening the tuberculosis and HIV collaborative activities, decentralizing the diagnostic and treatment centers to reach the periphery, providing women and young-age targeted interventions, stepping up early diagnosis and treatment initiation, improving nutritional supplementation to boost immunity, and providing prophylaxis to prevent opportunistic infections. Performing culture tests for all HIV infected smear-negative pulmonary tuberculosis patients is also recommended.

2.2. Literature on risk factors of survival of HIV/TB co-infected patients

Tarekegn (2011) conducted retrospective study in which a total of 632 patients (316 in ART and pre- ART cohort) were followed for a median of 32.9 months in Pre-HAART and 35.4 (IQR=23.6-36.5) months in HAART. The objective of the study was to identify factors that increase the risk of TB in PLWHIV. He used Cox proportional hazard analysis. The result of the

study indicated that WHO stage III or IV [HR=1.999 (95%CI: 1.025-3.896, P=0.042], being bedridden [HR=4.689, (95%CI: 1.715-12.819, P=0.003)], and having hemoglobin level less than 10mg/dl [HR=2.497,(95%CI: 1.098-5.679, P=0.036)] were factors associated with increased risk of TB in PLWHIV.

Catala *et al*. (2011) conducted a retrospective cohort study that included all HIV-infected TB patients reported in Barcelona between 1996 and 2006 with objective of estimating survival and to identify predictive factors and causes of death in a cohort of HIV infected TB patients in the era of HAART. based on the Kaplan-Meier estimator and Cox proportional hazards model by classifying causes of death as using the international classification of diseases (ICD)-9 and ICD-10, and classified as AIDS related or non-AIDS-related (that is, death because of other burden than AIDS). The results have shown that out of the 792 patients included, 341 (43.1%) died during the study period. Survival was worse among patients aged >30 years [HR 1.6, (95%CI 1.1-2.1)], inner-city residents [HR 1.3, (95%CI:1.1-1.7)], injecting drug users [HR 1.4, (95%CI: 1.1-1.8)], those with a non-cavitary radiological pattern [HR 1.5, (95%CI 1.0-2.2)], those with <200 CD4cells/mm^3 [HR 1.8, 95%CI:1.2-2.7)] and those diagnosed with AIDS prior to their TB episode [HR= 1.85,(95%CI 1.4-2.2)].

Prospective cohort study conducted on effect of antiretroviral therapy on survival of HIV/TB-infected patients in Ukraine by Andreychyn *et al.*(2013) of HIV patients who developed TB from January 2005 to December 2006 in a Zaporizhzhya AIDS center, and were tracked for 60 months after start HAART using Cox proportional hazards models and identified patients with a CD4 cell count <100 cells/mm3 had a 5-fold higher risk of mortality [HR= 5, 2; (95% CI 1.4-19, 4] and those with extra pulmonary tuberculosis 2-fold increased risk [HR =2.2, 95% CI: 1.8-3.2] of death for HIV/TB-infected patients in Ukraine.

The retrospective study, reviewed the causes of death for 331 patients who died of TB-HIV co-infection at Chiang Rai Prachanukroh Hospital from 2005 to 2008 by Kantipong *et al.* (2012) with main objective of causes of mortality among tuberculosis and HIV co-infected patients on causes of death for 331 patients using multivariate multinomial regression analysis. The study found that deaths in the first month (adjusted odds ratio [OR= 4.64, (95% CI: 2.49–8.63)], CD4 count >= 200 cells/mm^3 [OR =5.33, (95%CI: 1.05–26.10)], non-category TB treatment regimens [OR=5.23, 95%CI: 1.04–9.77)], and TB meningitis [OR=3.27, (95%CI:1.37–7.82)] were

significant predictors of confirmed TB deaths. Moreover, age over 45 years [OR=3, (95%CI 1.32–6.84)] and admission as an inpatient were predictors of death caused by neither TB nor AIDS-related opportunistic infections [OR=3.08, (95%CI 1.39–6.80)]. Additional analysis showed that non-Thai patients [OR=0.35, (95%CI 0.12–0.99)], those with an unknown CD4 count at TB diagnosis [OR=0.16,(95%CI: 0.08–0.33)], and those without an HIV diagnosis before TB treatment [OR= 0.32, CI: 0.18–0.59)] were less able to access antiretroviral therapy.

Retrospective cohort study was conducted between April, 2009 and January, 2012 by Sileshi *et al.* (2013) found despite the availability of free ART from health institutions in Northwest Ethiopia, mortality was high among TB-HIV co-infected patients, and strongly associated with the absence of ART during TB treatment. In addition cotrimoxazol prophylactic therapy remained important factor in reduction of mortality during TB treatment. The study also noted importance of early ART even at higher CD4 counts.

Study conducted on TB treatment outcomes among TB-HIV co-infections in Karnataka, India by Shastri *et al.* (2013) found that of the 6,480 adult HIV and TB co-infections registered 2010–2011 death rates among co-infected patients (15%) were twice as high as for TB patients under the program, though default and failure rates were lower and they concluded that co-infected patients already on ART demonstrated better TB outcomes in than those not on ART. Compared to those with TB only, co-infected patients had similar TB treatment success rates and lower rates of treatment default and failure. Integration of TB-HIV collaborative activities will strengthen our battle to control TB and HIV globally.

A retrospective study conducted by Hailu (2012) on thesis Survival and risk factors of HIV/TB co-infected patients under antiretroviral therapy in Ambo Hospital, Ethiopia with main objective of assessment of the survival and risk factors of HIV/TB co-infected patients in Ambo hospital using the Kaplan-Meier method was used to estimate the survival time and Cox's regression model to identify the covariates that have a statistical significant effect on the survival of HIV/TB co-infected patients and found that initial weight, TB site, WHO clinical stage, functional status and CD4 count are significant risk factors of survival of HIV/TB co-infected patients. Furthermore the patients with lower initial weight, lower CD4 count, WHO stage III and IV, being ambulatory and bedridden are associated with high risk factors.

Manda *et al.* (2013) on risk of death among HIV co-infected multidrug resistant tuberculosis patients, compared to mortality in the general population of South Africa with the methodology Poisson-based model adjusted for age, gender, year of diagnosis, TB history, and resistance to ethambutol, anti-TB inject able drugs and fluoroquinolones antibiotics for assessment of the excess mortality among HIV co-infected MDR-TB patients and excess hazard ratios (EHRs) were used to describe the effect of the predictors on net mortality, controlling for the general mortality in the South African population using available data from a cohort of 2079 MDR-TB patients enrolled in a standardized programmatic management of MDR-TB from 2000 to 2004 in South Africa. The study found of the death recorded on 1619 patients, of whom 367 (22.7%) had died within 2 years. Out of the 1413 patients that tested for HIV infection, 554 (39.2%) tested positive. Excess mortality was higher in HIV infected, compared to HIV uninfected, MDR-TB patients (adjusted excess hazard ratio, 5.6 [95% CI, 3.2-9.7]); in patients whose TB isolates' resistance to ethambutol and kanamycin was unknown (3.7 [2.1-6.2]) and (4.87 [1.9, 13.3]), respectively) vs. known. There were no differences in excess mortality between age and gender of the patient, year of diagnosis and TB history.

Zenner *et al.* (2013) on TB co-infection is associated with poor survival among HIV infected patients in England and Wales by examining deaths among a retrospective national cohort of adults (15 years +) diagnosed with HIV infection between 2000–2008 linked to the national TB databases and death records from the Office of National Statistics to mid-2010 by estimating hazard ratios (HR) using uni- and multi-variable Cox regression modeling to compare all-cause and AIDS-specific mortality by key demographic and clinical markers. They found total of 1,880 (4.3%) deaths observed among 44,050 HIV-diagnosed adults during 149,663 person-years of follow-up. 3,188 (7.2%) adults developed TB and HIV-TB cases accounted for 341 (18.1%) of all deaths of whom 270 (79.2%) were late presenters (CD4<200 cells/mm^3 at HIV diagnosis). One year mortality after HIV diagnosis was 45% overall and greater among HIV-TB cases (54%) and those with low CD4 counts at diagnosis (69% for CD4<50 cells/mm^3). TB co-infection and a low CD4 count at HIV diagnosis significantly increased the hazard of all cause mortality. In the fully adjusted model, the highest HR was among adults with extra pulmonary TB and pulmonary TB cases with CD4 count <100 at diagnosis.

2.3. Reviews on joint modeling approaches

Recently, joint modeling research has expanded very rapidly in Biostatistics and medical research. This type of models enables the simultaneous study of a longitudinal marker and a correlated time-to-event. Among them, the shared random effect models that define a mixed model for the longitudinal marker and a survival model for the time-to-event including characteristics of the mixed model as covariates received the main interest. Indeed, they extend naturally the survival model with time-dependent covariates and offer a flexible framework to explore the link between a longitudinal biomarker and a risk of event.

Some subjects drop out of the study before occurrence of the terminal event of interest. One may then wish to evaluate the relationship between time to dropout and the internal covariate. The Cox model is a standard framework for that purpose. Jean-Franc *et al.* (2002) addressed this problem in situations where the value of the covariate at dropout is unobserved. They suggested joint model which combines a first-order Markov model for the longitudinally measured covariate with a time-dependent Cox model for the dropout process by likelihood estimation of their model and show how estimation can be carried out via the EM-algorithm. They state that the suggested joint model may have applications in the context of longitudinal data with non ignorable dropout.

The accelerated failure time (AFT) model is an attractive alternative to the Cox model when the proportionality assumption fails to capture the relation between the survival time and longitudinal covariates. Several complications arise when the covariates are measured intermittently at different time points for different subjects, possibly with measurement errors, or measurements are not available after the failure time. Joint modeling of the failure time and longitudinal data offers a solution to such complications. Yi-kuan Tseng and others (2005) explored the joint modeling approach under the AFT assumption when covariates are assumed to follow a linear mixed effects model with measurement errors. Their procedure is based on maximizing the joint likelihood function where random effects are treated as missing data. They used Monte Carlo EM algorithm to estimate all the unknown parameters, including the unknown baseline hazard function and they considered case study of reproductive egg-laying data for female Mediterranean fruit flies and their relation to longevity demonstrate the effectiveness of the new procedure.

Ye, Lin and Taylor *et al.* (2008) used a penalized likelihood approach to joint modeling of longitudinal measurements and time-to-event data and they proposed to use an estimation procedure based on a penalized joint likelihood generated by Laplace approximation of a joint likelihood and by using a partial likelihood instead of the full likelihood for the event time data. The results of their simulation study showed that this penalized likelihood approach performs as well as the corresponding EM algorithm under a variety of scenarios, but only requires a fraction of the computational time. They also identified additional advantage of this approach which does not require estimation of the baseline hazard function and they applied the proposed procedure to a data set for evaluating the effect of the longitudinal biomarker PSA on the recurrence of prostate cancer.

Lee and Wang (2009) proposed methods for joint modeling of survival time and longitudinal data assuming a mixed-effects model with subject-specific change points for the longitudinal covariates and the proportional hazards model for the survival times and they develop the conditional score and corrected score estimators, which do not require the distributional assumption on the random effects or the change points and also they Showed that the two functional methods are equivalent asymptotically.

Kim and others (2011) propose to estimate all the parameters using the nonparametric maximum likelihood estimators (NPMLE) on their Joint Models of Longitudinal Data and Recurrent events with informative terminal event and they provide the simple and efficient EM algorithms to implement the proposed inference procedure. Asymptotic properties of the estimators are shown to be asymptotically normal and semi parametrically efficient. Finally, they evaluate the performance of the method through extensive simulation studies and a real-data application.

Lisa *et al.* (2011) investigated the known association between hemoglobin fluctuations and the survival of dialysis patients and their joint model agrees that those patients with higher hemoglobin levels have a greater survival rate. They indentified the significance of the shared parameter that links the two processes, and the reduction in the standard error of the parameter estimates when compared to independent model estimates, indicates the need for a joint analysis of for data compared to the use of independent models.

Mybery Sen and others (2013) on their briefly review of the shared random-effect model methodology and details of its implementation and evaluation through a real example from the

study of prostate cancer progression after a radiation therapy. In particular, different specifications of the dependency between the longitudinal biomarker, the prostate-specific antigen (PSA), and the risk of clinical recurrence are investigated to better understand the link between the PSA dynamics and the risk of clinical recurrence. They built different joint models are compared in terms of goodness-of fit and adequacy to the joint model assumptions but also in terms of predictive accuracy using the expected prognostic cross-entropy. In-deed, in addition to better understand the link between the PSA dynamics and the risk of clinical recurrence, they used perspective in prostate cancer studies is to provide dynamic prognostic tools of clinical recurrence based on the biomarker history.

Hyun J. Lim *et al.* (2013) demonstrated the use of joint modeling in analysis of an HIV dataset with CD4+ count measurements and survival time. In their joint modeling, they combined a linear Gaussian random effects sub-model for the repeated CD4+ count measurements and Cox or Weibull survival sub-model, linked through their shared dependence on the latent variable and they showed that the hazard rate of death depended on the longitudinal progression of CD4+ counts, i.e., a patient's baseline CD4+ count and the rate of change in CD4+ counts significantly impact on his or her survival time.

Rizopoulos(2014) presented the capabilities of the R package JMbayes for fitting these models under a Bayesian approach using Markon chain Monte Carlo algorithms. JMbayes can fit a wide range of joint models, including among others joint models for continuous and categorical longitudinal responses, and provides several options for modeling the association structure between the two outcomes. In addition, this package can be used to derive dynamic predictions for both outcomes, and offers several tools to validate these predictions in terms of discrimination and calibration. All these features are illustrated using a real data example on patients with primary biliary cirrhosis. In general joint analysis of longitudinal measurements and survival data has received much attention where longitudinally measured markers related to the survival status in recent years.

3. METHODOLOGY

3.1. Study area

The study was conducted at Jimma University Specialized Hospital which is located in Jimma town is located in Oromia National Regional State, Jimma town is located at a distance 325 Km from Addis Ababa which is the center of the country or Ethiopia. Its astronomical location is 7º 4' north latitude and 36º 5' east longitude. The town was founded in 1837 and one of the reform towns in the region and has a city administration, municipality and 13 Kebelles. According to the national population and housing census carried out in 2007, the population of the town was 120,960. Out of this 60,824 (50%) were male and 60,136 (50%) were female. Regarding age distribution 37,055 (31%) were within the age group of 0-15 years, 80,083 (66%) 16-60 years, and 3,822 (3%) 61 years and above. The population growth rates at medium 3.75%, while household size in the town was calculated to be 4. (www.mwud.gov.et/web/jimma).

3.2. Data source

The data for the study was obtained from JUSH from HIV and TB outpatient Clinic, South West of Ethiopia. Both the longitudinal and survival data are extracted from the patient's chart which contains epidemiological, laboratory and clinical information of all HIV/ TB after identification of patients who had the co-infection from ART follow-up.

3.2.1. Study population

All HIV/TB co-infected patients who are at an age of 18 years old and above placed under ART follow up any time in between first February 2009 to first July 2014 in JUSH are considered in the study. Among 856 total co-infected patients during the time period 254 patients who were 18 years and older having at least one CD4 count measurement since the patients are from HIV and TB clinic after first February 2009 and before first July 2014 were considered for the study.

3.3. Variables of the study

3.3.1. Response variables

Two outcome variables are considered for the study was; the longitudinal measured continuous outcome variable which is a bio marker for the co-infected patient and the survival outcome variable. The longitudinal continuous outcome which is a bio marker variable was the number of CD4 cell counts per mm^3 of blood which was measured within six months interval.

The survival outcome variable was the survival time (time-to-death) of the co-infected patients. Time-to-death of the patients was the time from date of co-infection to the death of the patients during the time period which was measured in days. Patients who lost the follow; transferred to another Hospital before experience the event and the patients who are still on ART follow up to first July 2014 is considered as the censoring.

3.3.2. Covariates

The independent covariates considered for the separate longitudinal and survival modeling as well for the joint modeling are listed in the following table:

Table 1: List of independent covariates

Variables	Values of variables	Type
Age	Years(baseline)	Continuous
Weight	Kilogram(time vary)	Continues
Marital status	Single, married, separated, windowed and divorced	Categorical
Residence	Rural and urban	Categorical
Educational level	Not educated, primary, secondary and tertiary	Categorical
Working time	Par timer, working full time and un employed	Categorical
Use of alcohol	use and do not use	Categorical
Smoking	Smoker and non smoker	Categorical
Use of soft drug	Use and do not use	Categorical
Type of tuberculosis	Pulmonary TB and extra pulmonary TB	Categorical
WHO clinical stage	Stage I,II,III and IV	Categorical
Functional status	Working, ambulatory and bed ridden	Categorical
Religion	Muslim, orthodox and protestant	Categorical
Sex	Female and male	Categorical

Notice that WHO Clinical Stage which is classified into four; I, II, III and IV; where Stage I indicates asymptomatic disease, Stage II indicates mild disease, Stage III indicates advanced disease and Stage IV indicates severe disease. Hence disease severity increases from Stage I to

Stage IV. Functional Status of the patients is also categorical covariate with three categories: Working, Ambulatory and Bedridden. Working patients are those patients who can able to work day to day while ambulatory patients are those patients who can able to work some time but bedridden patients cannot able to work due to the disease. Working time is also another categorical covariates with four categorical groups' part time worker who works part time; full time worker; not working because of medical illness and unemployed who do not have work.

3.4. Methods of data analysis

In order to extract information from the given data the collected data was analyzed using different methods depending on the objective of study to give a certain conclusion about the collected data. The same was done in this study; both descriptive and inferential data analyses were considered to analyze the collected data.

Descriptive data analysis: In order to describe the character of the HIV/TB co-infected patients the collected data was analyzed by using descriptive techniques that visualize the collected data in descriptive manner.

Inferential data analysis: To infer about the population inferential statistics was employed. Among the inferential techniques different longitudinal; survival and joint modeling approach was considered for the study.

3.4.1. Longitudinal data modeling

Longitudinal responses may arise in two common situations; one is when the measurements taken from the same subject at different times and the other is when the measurements taken on related subjects (clusters). In both of these cases, the measurements are likely to be correlated. Therefore; longitudinal model considers two sources of variations which is known to be; within-subject variation which is the variation in the measurements within each subject and between-subject variation; which is the variation in the data between different subjects.

Modeling within-subject variation allows studying changes over time, while modeling between-subject variation allows understanding differences between subjects.

3.4.1.1. Exploratory data analysis

Data exploration is a very important tool to fit of appropriate models and to look at pattern of data over time. It show as much of the raw data as possible rather than summarized values,

highlight aggregate patterns of scientific interest. Some of the data explorations used for the study includes: individual profiles; for identification of within and between variability of CD4 count measurement of the patients at different time points, the average evolution; for identification the mean structure of the CD4 count measurements over time and the variance evolution; for identification of the variance structure of CD4 count measurement taken at different time points. In all exploration graphical inspection can be used by connecting each value computed at each time point separately. Since the data was not balanced loess smoothing was used instead that give us visualization of data in order to choose fixed-effects effects and random effects for the linear mixed model.

3.4.1.2. Linear mixed model (LMM)

Linear mixed models (LMM) is statistical models for longitudinal or repeated-measures studies, in which subjects are measured repeatedly over time or under different conditions and measurements in which the residuals are normally distributed but may not be independent (have a correlations) this LMM is proposed by Laird and Ware (1982) on which their work was based on Harville (1977), included a unified approach using growth models and repeated-measures models for the sequence of the longitudinal measurements $y_{i1}, y_{i2,}..., y_{ini}$ for the i[th] subject at times t_{i1} , $t_{i2,}...,t_{ini}$ is modeled as:

$$\mathbf{y}_i = \mathbf{X}^T(t)\boldsymbol{\beta} + \mathbf{Z}^T{}_i(t)\mathbf{b}_i + \boldsymbol{\varepsilon}_i$$

$$\mathbf{y}_i = \boldsymbol{\mu}_i(t) + \mathbf{U}_{1i}(t) + \varepsilon_i \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(1)}$$

$$\mathbf{b}_i \sim N(\mathbf{0},\mathbf{D}), \varepsilon_i \sim N(\mathbf{0},\boldsymbol{\delta}_\varepsilon{}^2\mathbf{I})$$

Where;

$\mathbf{y}_i$ is n_i x1 dimension of the response

$\boldsymbol{\beta}$ is Px1 dimensional of vector of fixed effects

$\mathbf{b}_i$ is qx1 dimension of vector of random effects

X(t) is $n_i$xp dimension combination of time varying and fixed matrix of covariates

$\mathbf{Z}_i$(t) is a matrix of kxq covariates of random effects

$\boldsymbol{\varepsilon}_i$ is n_i dimension of vector of within group errors which is normally distributed

In the above model (1) $\mu_i(t)$ represent is the mean response (mean structure part) and $\mathbf{U}_{1i}(t) = \mathbf{Z}_i(t)^T\mathbf{b}_i$ incorporates the random effects part which is the true individual level CD4 trajectories

after they have been adjusted for the overall mean. Here, in mixed effects models, random effects $\mathbf{b}_i$ is introduced for each subject to incorporate the correlation between the repeated measurements within subject. Since each subject shares the same random effects, the measurements within subject are correlated. Moreover the random effects facilitate subject specific inference.

In general the above model (1) specifically incorporates both sources of variations: it uses random effects or subject effects to represent deviations of subject longitudinal trajectories from the population average. Thus, a mixed effects model allows subject specific inference, in addition to standard population average inference and the model was fitted in two stages in which the first stage involves the fitting of the appropriate fixed effect model which is developed using linear model and the second stage involves the selection of appropriate random effects parts for the selected fixed effects.

3.4.1.2.1. Estimation of linear mixed model

Estimation is more difficult in the mixed model than in the general linear model. This is because in mixed model estimation of random effects and covariance structure of the random error is necessary besides to the fixed effect. The maximum likelihood (ML) was considered for the estimation of the parameters of the model. The maximum likelihood estimation method finds the parameter estimates that are most likely to occur given the data. The parameter estimates are derived by maximizing the likelihood function, which is a mathematical expression that describes the joint probability of obtaining the data expressed as a function of the parameter estimates.

Maximum likelihood estimation: the maximum likelihood (ML) method used to estimate **D** and **Σ**. let **V** be the variance of the response the maximum likelihood provides unbiased estimators under normal errors. The log-likelihood function for observed responses is given by:

$$L(\mathbf{D}, \mathbf{\Sigma}) = -\frac{1}{2}\log|\mathbf{Y}| - \frac{1}{2}(\mathbf{M})^{T}\mathbf{Y}^{-1}\mathbf{M} - \frac{n-p}{2}\log(2\pi) \quad \ldots\ldots(2)$$

Where; $\mathbf{M} = \mathbf{Y} - \mathbf{X}(\mathbf{X}^{T}\mathbf{V}^{-1}\mathbf{X})^{-1}\mathbf{X}^{T}\mathbf{V}^{-1}\mathbf{Y}$, and p is the rank of **X** estimating fixed effect ($\boldsymbol{\beta}$) and random effect (**b**) parameters in the Mixed Model. Once getting estimates values of **D** and $\boldsymbol{\varepsilon}$, which are denoted by $\hat{\mathbf{D}}$ and $\hat{\boldsymbol{\varepsilon}}$ hat respectively the estimated values of random effect and fixed

was based on these two estimated values (Proust-Lima,2005).The computation of values parameters was based on R-statistical soft ware version 3.1.0.

3.4.2. Survival data modeling

Survival models seek to explain how the risk, or hazard, of an event occurring at a given time is affected by covariates of theoretical interest. In a single event analysis, the survival function is defined as the probability that the survival time is greater or equal to t which is given by:

$$S(t) = P(T \geq t) = \int_{t}^{\infty} f(t)dt \text{ for } t \geq 0 \ldots\ldots(3)$$

Where; *f(t)* is the probability density function of event time T for continues case and the integration value becomes summation when we have discrete time event. Whereas the hazard rate is the instantaneous risk of experiencing the event at a given time given that it has survived (i.e., not experienced the event) up to that time which is given by:

$$\lambda(t) = Lim_{\Delta t \to 0} \frac{P(t \leq T < \Delta t / T \geq t)}{\Delta t}, t \geq 0$$

$$\lambda(t) = \frac{f(t)}{S(t)} = -\frac{d \log(S(t))}{dt} \ldots\ldots(4)$$

Or in other words hazard function is the probability that an individual will experience an event.

Very often, time-to-event data will be grouped into strata (or clusters), such as clinical sites, geographic regions, time and so on. In this setting, a hierarchical modeling approach using stratum-specific frailties is often appropriate, that is a mixed model with random effects (the frailties) corresponding to a stratum's overall health status. In general, survival techniques can be applied to a wider range of different situations, subject to the three necessary requirements as stated by Cox and Oaks (1984); firstly a well defined time origin must be determined, then a scale for measuring the progress of time must be defined, and finally the exact definition of failure must be clear.

Basic definition of survival time modeling

3.4.2.1. Non-parametric survival methods

Preliminary analysis of the data using non-parametric methods provides insight into the shape of the survival function for each group and get an idea of whether or not the groups are proportional, i.e., if the estimated survival functions for two groups are approximately parallel

(do not cross). The Kaplan-Meier estimator is a nonparametric estimator of the survival function (Kaplan and Meier (1958)) which is not based on the actual observed event and censoring times, but rather on the order in which events occur. This principle of nonparametric estimation of the survival function is to assign probability to and only to uncensored failure times. Suppose there are n observations, $t_1, ..., t_n$, with corresponding censoring indicators, $\delta_1 ,...,\delta_n$. Let the number of distinct event times be r ($r \le n$), with the ordered event times given by $t_{(1)} <, ... ,<t_{(r)}$ and corresponding number of events $d_{(1)} ,...,d_{(r)}$. And also let $R(t_{(j)})$ denote the risk set at the event time $t_{(j)}$, i.e., the set of subjects that did not yet experience the event and were not yet censored before time $t_{(j)}$ and thus still at risk for the event at that time. Therefore, the Kaplan-Meier estimate of the survival function at time t is given by:

$$\hat{S}(t) = \prod_{i=1}^{k}\left(\frac{R(t_{(j)}) - d_{(j)}}{R(t_{(j)})}\right), \text{ for } t_{(j)} < t < t_{(j+1)} ,\ k=1,2,...,r \ldots\ldots(5)$$

3.4.2.1.1. Log-rank test

The estimated Kaplan- Meier survival curves shows the pattern of one survivorship function lying above another, this means the group defined by the upper estimated curve lived longer, or had a more favorable survival experience than the group defined by the lower estimated curve. But, the statistical question is whether the observed difference seen on the curve is significant. One way of which give an answer for such statistical question is long rank test which is the most widely used to test the significance difference between the estimated Kaplan-Meier survival curves where the its computed statistics is given by:

$$\frac{\left(\sum_{i=1}^{m}(d_{1i} - \hat{e}_{1i})\right)^2}{\sum_{i=1}^{m}\hat{v}_{1i}} ,\ \hat{e}_{1i} = \frac{n_{1i}d_i}{n_i} \text{ and } \hat{v}_{1i} = \frac{n_{0i}n_{1i}d_i(n_i - d_i)}{n_i^2(n_i - 1)}$$

Where;

m is the number of rank-ordered failure (death) times.

n_{0i} is the number of individuals at risk at observed survival time $t_{(i)}$ in group 0

n_{1i} is the number of individuals at risk at observed survival time $t_{(i)}$ in group 1

d_{0i} is the number of observed deaths in group 0

d_{1i} is the number of observed deaths in group 1

n_i is the total number of individuals or risk prior to time $t_{(i)}$

d_i is the total number of deaths at time (i)

The computed test statistics have a chi-square distribution

3.4.2.2. Semi parametric survival model: Cox PH Model

In survival analysis, to determine if the variation in subjects' survival experience is partially explained by covariates or to find any possible relationship between survival times and important covariates, a popular approach is to model the hazard function rather than the mean of the survival times as in the classical regression models. That is, survival models are most often defined in terms of the hazard function. Since a hazard function may be complicated, a parametric assumption can be avoided and the hazard function allowed being nonparametric. Such survival models with no distributional assumption of the hazard function are termed as semi-parametric model which is proposed by Cox (1972). The widely used semi-parametric survival regression model is the Cox proportional hazards (PH) model in which the hazard at time t can be expressed as:

$$\lambda_i(t) = \lambda_0(t)\exp(\mathbf{W}^T\boldsymbol{\gamma}) \quad \text{..... (6)}$$

Where;

$\lambda_0(t)$ is the base line hazard function

W is the matrix of base line covariates which affects the hazard function and

$\boldsymbol{\gamma}$ is the vector of parameters for the covariates.

If all of the covariates are zero the model (2) above become $\lambda_i(t) = \lambda_0(t)$ because of this we call the term $\lambda_0(t)$ the baseline hazard function. In this model, no distributional assumption is made for the survival time; the only assumption is that the hazards ratio $\psi = \frac{\lambda_i(t)}{\lambda_j(t)}$ does not change over time (i.e., proportional hazards) that is why this model is also known as semi-parametric model.

The parameter of the Cox proportional hazard model refers to the hazard ratio of one group in comparison to the other groups for categorical covariates and change in hazard ratio with a unit change of the covariate for the continuous variables when other covariates are fixed. The

elements of (covariates in survival model) **W** may or may not the same to that of longitudinal matrix covariates or **X** and the change in hazard ratio for the continuous covariate is given by:

$$\frac{\lambda(t, w_k + 1)}{\lambda(t, w_k)} = \frac{\exp(\gamma_1 w_1 + ... + \gamma_k (w_k + 1) + ...)}{\exp(\gamma_1 w_1 + ... + \gamma_k (w_k) + ...)} = \exp(\gamma_k)$$ which represents change (equivalently, $\exp(\gamma_1)$*100% percentage change) hazard function with unit change in covariate provided that other covariates remains fixed. For a categorical covariate **W** with *l* levels, the model contains (*l*−1) dummy variables defined as $\mathbf{Z}_i = 1$ if $\mathbf{W} = i$, and 0 otherwise for i = 1, 2,..., $l - 1$. Let $\gamma_1 \ldots \gamma_{l-1}$ denote the coefficients in front of the appropriate dummy variables. Then the ratio of the hazard of two subjects, one with **W** at level j and the other with **W** at level k (j, k = 1,2,..., $l - 1$), provided the values of all other covariates for these subjects are the same, the hazard ration between these two categories is given by:

$$\frac{\lambda(t, z_i)}{\lambda(t, z_k)} = \frac{\exp(\gamma_j)}{\exp(\gamma_k)} = \exp(\gamma_j - \gamma_k)$$ Which represents hazard functions for subjects at level j and at level k of the covariate (j, k = 1,2,..., $l - 1$), provided the other covariates have equal values. There are also some assumptions of the Cox proportional hazards model to be fulfills that is; The ratio of the hazard function for two individuals with different sets of covariates does not depend on time, time is measured on a continuous scale and censoring occurs randomly.

3.4.2.3. Parametric survival models

Parametric survival models are models requiring the specification of a probability distribution for the survival times and survival times needs to follow a certain parametric distribution. Parametric models assume that the survival data follow some probability distribution. The effect of covariates on survival time is through the conditional hazard function. The PH model of the parametric survival model is same to model (6) but in parametric PH model, the baseline hazard function $\lambda_0(t)$ is modeled parametrically which have a certain parametric distribution which represents the base line hazard function for parametric survival model when all covariates are zero and the influence of covariates are multiplicative through $\exp(\mathbf{W}^T \boldsymbol{\gamma})$.The proportional hazard for the different individuals for parametric model also is given by:

$\frac{\lambda(t/\mathbf{W}_j)}{\lambda(t/\mathbf{W}_k)} = \frac{\lambda_0(t)\exp(\mathbf{W}_j{}^T\boldsymbol{\gamma})}{\lambda_0(t)\exp(\mathbf{W}_k{}^T\boldsymbol{\gamma})} = \exp(\mathbf{W}_j - \mathbf{W}_k)^T\boldsymbol{\gamma}$ this is constant. If the proportional hazard is no longer valid an alternative method is survival regression modeling is accelerated failure time (AFT) model since model does not require the proportional hazard assumption. In AFT model we consider log scale of time which is given by:

Log(T)= $\mathbf{W}^T\boldsymbol{\gamma} + \sigma\zeta_i$ ……(3)

Where;

ζ_i~F and F is parametric error distribution and σ is scale parameter.

Different distributional choices for ζ_i lead to different models and the most common choice for the distribution of ξ_i is the Gumbel distribution which is an extreme value distribution. If ζ_i follows the Gumbel distribution, the survival time T_i follows a Weibull distribution. If ζ_i follows the Gumbel distribution and σ = 1, then it will be reduced to an Exponential model and another common choice for the distribution of ζ_i is the standard normal distribution N(0,1). If ζ_i follows N(0,1), the survival time T_i follows a log-normal distribution. The logistic distribution is also another possible choice if ζ_i follows a logistic distribution, the survival time T_i follows a log-logistic distribution and the hazard function of the AFT model is given by:

$\lambda(t/\mathbf{w}) = \lambda_0(t\exp(-\boldsymbol{\gamma}^T\mathbf{W}))\exp(-\boldsymbol{\gamma}^T\mathbf{W})$ …… (7)

We deal the effect of the covariates through $\exp(-\boldsymbol{\gamma}^T\mathbf{W})$ that is the time scale is changed by factor of $\exp(-\boldsymbol{\gamma}^T\mathbf{W})$.

3.4.2.4. Estimation methods of survival models

Semi parametric model parameter estimation method: In Cox proportional hazards model we can estimate the vector of parameters $\boldsymbol{\gamma}$ without having any assumptions about the baseline hazard $\lambda_0(t)$. As a consequence, this model is more flexible and an estimate of the parameters can be obtained easily. Consider n independent individuals, the data that we need for the Cox proportional hazard model is represented by (T_i, δ_i, W_i) i= 1, 2,…,n, Where, t_i = the survival time for the i^{th} individual

$\boldsymbol{\delta}_i$ = an indicator of censoring for the i^{th} individual given by 0 for censored and 1 for event

$\mathbf{W}_i$ = a vector of covariates for individual i (w_1,w_2,…,w_p)

The full likelihood for right censored data can be constructed as

$L(\boldsymbol{\gamma}) = \prod_{i=1}^{n} h(T_i, \mathbf{W}, \boldsymbol{\gamma})^{\delta i} S(T_i, \mathbf{W}, \boldsymbol{\gamma})$ ……(8)

Where;

$h(t_i, W_i, \gamma) = h_o(t_i)\exp(\boldsymbol{\gamma}^T \mathbf{W}_i)$ is the hazard function for individual i.

$S(t_i, W, \gamma) = (S_0(t_i))^{\exp(\boldsymbol{\gamma}^T \mathbf{W})}$ is the survival function for individual i.

It follows that $L(\boldsymbol{\gamma}) = \prod_{i=1}^{n} (h_0(t_i)\exp(\boldsymbol{\gamma}^T \mathbf{W}))^{\delta i} (S_0(t_i))^{\exp(\boldsymbol{\gamma}^T \mathbf{W})}$

The full maximum likelihood estimator of $\boldsymbol{\gamma}$ can be obtained by differentiating $L(\boldsymbol{\gamma})$ with respect to the components of $\boldsymbol{\gamma}$ and the base line hazard. This implies that unless we explicitly specify the base line hazard, as in the case of parametric PH, we cannot obtain the maximum likelihood estimators for the full likelihood. To avoid the specification of the base line hazard, (Cox, 1972) proposed a partial likelihood approach that treats the baseline hazard as a nuisance parameter and removes it from the estimating equation. Instead of constructing a full likelihood, we consider the probability that an individual experiences an event at time t_i given that an event occurred at that time.

Partial likelihood: Let R_i denote the set of individuals at risk at time just prior to $t_{(i)}$. Assume that for the present case there is only one failure at time t_i , i.e, no ties. The probability that individual i with covariates $\mathbf{w}_i$ is the one who experience the event at time $t_{(i)}$ is given by:

$\frac{h(t,W)}{\sum_{j \in R_{t(i)}} h(t,W_i)}$ and under the proportional hazards assumption on equation, the ratio

$\frac{h_0(t)\exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}{\sum_{j \in R_{t(i)}} h_0(t)\exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}$ shows the contribution to the partial likelihood at each event time $t_{(i)}$ by the individuals with covariate w_i in risk set $R_{t(i).}$ where $R_{t(i)}$ is the overall subjects in the risk set at time $t_{(i)}$ but by eliminating the base line hazards function, the above equation becomes

$\frac{\exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}{\sum_{j \in R_{t(i)}} \exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}$

Thus the partial likelihood is the product over all failure time $t_{(i)}$ for i = 1,2,…,m of the conditional probability to give partial likelihood

$L_p(\boldsymbol{\gamma}) = \prod_{i=1}^{m} \frac{\exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}{\sum_{j \in R_{t(i)}} \exp(\boldsymbol{\gamma}^T \mathbf{W}_i)}$ ……(9)

The product is over the m distinct ordered survival times and w_i denote the value of the covariate for the subject with ordered survival time $t_{(i)}$. The log partial likelihood function is

$l_p(\boldsymbol{\gamma})=\sum_{i=1}^{m}[\boldsymbol{\gamma}^T\mathbf{W}_i - \ln(\sum_{j\in R_{t(i)}}\exp(\boldsymbol{\gamma}^T\mathbf{W}_i))]$ ……(10)

under this setting the maximum partial likelihood estimator obtained by differentiating the function with respect to $\boldsymbol{\gamma}$, setting the derivative equal to zero and solving for the unknown parameters. But the partial likelihood derived above is valid when there are no ties in the data set. In most real situations tied survival times are more likely to occur. To handle this fact, partial likelihood algorithms have been adopted to handle ties. There are different methods to estimate regression parameters when there are ties. The most popular and easy approaches are Breslow's and Efron approximation, in this study the Breslow approximation which is the default value of ties handling in R-soft were used in case of ties.

Estimation of parameters for parametric survival model: In parametric modeling, maximum likelihood estimation method commonly used estimation of parameters of the model. For parametric regression model the with base line hazard function and with vector of regression coefficient $\boldsymbol{\gamma}$ including the intercept parameter suppose that the random variable and suppose that (t_i,δ_i, W_i) come from the parametric hazard rate regression with parametric distribution. The likely hood function that maximizes the parameter $\boldsymbol{\gamma}$ is given by:

$$L(\boldsymbol{\theta})=\prod_{i=1}^{n}(\lambda_0(t)\exp(\mathbf{W}^T\boldsymbol{\gamma}))^{\delta_i}\exp(-\int_0^t\lambda_0(u)\exp(\mathbf{W}^T\boldsymbol{\gamma})du \quad \ldots\ldots (11)$$

The likely hood function can be also constructed in terms of AFT perspective which is given by:

$$L(\boldsymbol{\theta})=\prod_{i=1}^{n}\{\lambda_0(t\exp(-\mathbf{W}^T\boldsymbol{\gamma}))\exp(-\mathbf{W}^T\boldsymbol{\gamma})\}^{\delta_i}\exp(-\Lambda_0(t\exp(-\mathbf{W}^T\boldsymbol{\gamma})) \quad \ldots\ldots (12)$$

The estimation of parameters for the model was based on the full likelihood function in both cases and the required parameters was obtained by maximizing the full log likelihood function with respect to the required parameter and R-soft ware version 3.1.0 were used for all computations.

3.4.3. The joint modeling structure

In joint modeling of longitudinal data and survival data, the main focus may be either the longitudinal model, or the survival model, or both models, depending on objectives of the study. When the main focus is on the one model, the other model is then secondary so its parameters may be viewed as nuisance parameters. In this case, one should focus on correct specification of the main model and simplify the secondary model to reduce the number of nuisance parameters

and avoid potential parameter non-identifiable (Lang Wu, 2009). If both models are of primary interest, we may reduce the number of other secondary parameters. The main aim of this study was also to associate longitudinal model process with survival model process with primary interest of both models using shared parameters association structure. The main goal was to understand the association between the two processes that is to understand the association between the survival time of HIV/TB co-infected patients and characteristics longitudinally measured CD4 count measurement process of the co-infected patients. In order to avoid potential bias in some cases, the longitudinal and survival models may be linked through shared parameters leading to so-called shared parameter models.

3.4.3.1. The longitudinal sub-model specification

The main goal, in this study, is to jointly model the longitudinal CD4 measurement process and time-to-death of HIV/TB co-infected patients, with a special attention to the effect of CD4 measurements on the risk of death of co-infected patients. The longitudinal sub-model which is given by linear mixed model (1) is as follows:

$$\mathbf{y}_i = \mathbf{X}^T(t)\boldsymbol{\beta} + \mathbf{Z}_i{}^T(t)\mathbf{b}_i + \boldsymbol{\varepsilon}_i$$
$$\mathbf{y}_i = \boldsymbol{\mu}_i(t) + \mathbf{U}_{1i}(t_{ij}) + \boldsymbol{\varepsilon}_i$$
$$\mathbf{b}_i \sim N(\mathbf{0}, \mathbf{D}), \varepsilon_i \sim N(\mathbf{0}, \boldsymbol{\delta}^2\mathbf{I})$$

Where;

$\mathbf{y_i}$ is observed responses

$\boldsymbol{\beta}$ is a p dimensional vector of fixed effects

$\mathbf{b}_i$ is a q dimensional vector of random effects

$\mathbf{X}(t)$ is a matrix of (size n $*p_i$) fixed effects possibly time-varying covariates

$\mathbf{Z}_i(t)$ is a matrix of (size n* q_i) random effects covariates and $\boldsymbol{\varepsilon}_i$ is an n_i dimensional vector of within group errors with a Gaussian distribution

$\boldsymbol{\mu}_i(t)$ is the mean response (mean structure part) and $\mathbf{U}_{1i}$ (t_{ij}) incorporates the random effects part.

3.4.3.2. The survival sub-model specification

After specifying the longitudinal sub-model, the next aim is to associate the true and unobserved value of the longitudinal outcome (CD4 count measurement) at time t with the survival outcome via shared parameters. As shown before, both of the separate and joint models assume the

longitudinal sub-model has the form similar to the usual linear mixed effects model, while the survival model in the joint model includes a shared parameter association function $\mathbf{U}_{2i}(t)$ the event time model is based on an approximation to the hazard function, the usual partial likelihood for the Cox model which is proposed by Tsiatis *et al.* (1995) which is given by:

$$\lambda(t/\mathbf{w}) = \lambda_0(t)\exp(\mathbf{W}^T\boldsymbol{\gamma} + \mathbf{U}_{2i}(t)) \quad \ldots\ldots (13)$$

Where;

$\lambda_0(t)$ is the base line hazards function and this model(5) is differ from the separate survival with inclusion of $\mathbf{U}_{2i}(t)$ defines the nature association structure of the parameters between the two processes and distributed as the multivariate function of shared parameters. The three association structure values of $\mathbf{U}_{2i}(t)$ proposed for this study were:

I. $\mathbf{U}_{2i}(t) = \boldsymbol{\alpha} m_i(t)$

II. $U_{2i}(t) = \boldsymbol{\alpha}^T \mathbf{b}_i$

III. $U_{2i}(t) = \boldsymbol{\alpha}^T(\boldsymbol{\beta}_b + \mathbf{b}_i)$

Where;

$m_i(t)$ denotes current underlying value of the longitudinally measured CD4 count marker processes at the same time point;$\boldsymbol{\alpha}$ measures the strength of association vectors between two processes; $\mathbf{b}_i$ is random effect parameters of the longitudinal part and $\boldsymbol{\beta}_b$ is fixed effect parameters corresponding to the random effects. The appropriate shared parameters association structure for the joint modeling that appropriately associate the longitudinally measured CD4 count measurement process and time-to-death of HIV/TB co-infected patient was selected based on DIC score.

3.4.4. Joint model estimation methods

Given the random effects, the longitudinal process is assumed to be independent from the event time. Let $\boldsymbol{\Theta}_1$ and $\boldsymbol{\Theta}_2$ be the vector of parameters defined in linear mixed model and survival model respectively. Using the assumption of independence between the longitudinal and the survival processes conditionally to the random effects their joint density function is given by:

$$f(\mathbf{Y},\mathbf{T},\boldsymbol{\delta}/\boldsymbol{\Theta}_1,\boldsymbol{\Theta}_2) = \int f_Y(Y_i/\boldsymbol{\Theta}_1,\boldsymbol{\eta}_i) f_T(T,\delta/\mathbf{Y},\boldsymbol{\Theta}_2,\boldsymbol{\eta}_i) f(\boldsymbol{\eta}_i) d\boldsymbol{\eta}_i \quad \ldots\ldots (14)$$

Where their joint log likely hood function is given by:

$$l(\mathbf{Y},\mathbf{T},\boldsymbol{\delta}/\boldsymbol{\Theta}_1,\boldsymbol{\Theta}_2)=\log\left[\prod_{i=1}^{N} f_Y(\mathbf{Y}_i/\boldsymbol{\Theta}_1,\boldsymbol{\eta}_i)(\lambda(\mathbf{T}/\mathbf{Y}_i)^{\delta_i} S(\mathbf{T}/\mathbf{Y}_i) f(\boldsymbol{\eta}_i) d\boldsymbol{\eta}_i\right] \quad \ldots\ldots\ldots\ldots\ldots\ldots (15)$$

Where;

$\lambda(T/\mathbf{Y}_i)$ is the survival hazard function

$S(T/Y_i)=\exp(-\int_0^t \lambda(u/Y_i)du)$ is the survival function and f_Y and $f(\eta_i)$ represents the density function for the longitudinal and shared parameters respectively

The computation these likelihood inference based on the above joint likelihood can be highly intensive and the estimation of the parameters are based on Bayesian approach using Markov chain Monte Carlo (MCMC) algorithm with R-statistical software under JMpakage.

3.4.4.1. Prior and posterior distributions

Under Bayesian approach, model parameters are treated as random variables and assigns probability to each, which is the major difference to the likelihood approach. They assume prior distributions for the parameters. Bayesian estimation and inference is based on the posterior distribution which is the conditional distribution of unobserved quantities given the observed data and Bayee's theorem is used to construct the posterior distribution. Let **y** be the observed data and **θ** a vector of unknown parameters. f **(θ | y)** is the posterior probability distribution of the parameter **θ** under Bayesian approach is given by:

$$f(\boldsymbol{\theta}/\mathbf{y})=\frac{f(\mathbf{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})}{f(\mathbf{y})}=\frac{f(\mathbf{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})}{\int f(\mathbf{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})d\boldsymbol{\theta}}\propto f(\mathbf{y}|\boldsymbol{\theta})f(\boldsymbol{\theta}) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (16)$$

Where;

$f(\boldsymbol{\theta}|\mathbf{y})$ is is the posterior probability distribution of **θ**

$f(\mathbf{y}|\boldsymbol{\theta})$ is the likelihood function

$f(\boldsymbol{\theta})$ is the prior probability distribution of **θ**

The expression for the posterior distribution of the model parameters is derived under the assumptions that given the random effects, both the longitudinal and event time process are assumed independent, and the longitudinal responses of each subject are assumed independent. Formally we have,

$$f(\mathbf{y}_i, \mathbf{T}_i, \boldsymbol{\delta}_i \mid \mathbf{b}_i, \boldsymbol{\theta}) = f(\mathbf{y}_i \mid \mathbf{b}_i, \boldsymbol{\theta}) f(\mathbf{T}_i, \boldsymbol{\delta}_i \mid \mathbf{b}_i, \boldsymbol{\theta})$$

$$f(\mathbf{y}_i \mid \mathbf{b}_i, \boldsymbol{\theta}) = \prod_{j=1}^{n_i} f(y_{ij} \mid \mathbf{b}_i, \boldsymbol{\theta})$$

Where; $\boldsymbol{\theta}$ denotes the full parameter vector, and f(.) denotes an appropriate probability density function. Under these assumptions the posterior distribution is analogous to:

$$f(\boldsymbol{\theta}, \mathbf{b}) \propto \prod_{i=1}^{N} \prod_{j=1}^{n_i} f(y_{ij} \mid b_i, \boldsymbol{\theta}) f(T_i, \delta_i \mid b_i, \boldsymbol{\theta}) f(b_i, \boldsymbol{\theta}) f(\boldsymbol{\theta}) \quad \text{.....(17)}$$

Where;

$f(y_{ij} \mid b_i, \boldsymbol{\theta}) = \exp\{\lfloor y_{ij}\psi_{ij}(b_i) - c\{\psi_{ij}(b_i)\}\rfloor / a(\varphi) - d(y_{ij}, \varphi])\}$ With φ_{ij}(bi) and φ denoting the natural and dispersion parameters in the exponential family, respectively, c(.),a(.) and d(.) are known functions specifying the member of the exponential family, and for the survival part.

$$f(T_i, \delta_i \mid b_i, \boldsymbol{\theta}) = \lambda(T_i \mid \Lambda(T_i))^{\delta_i} s(t \mid \Lambda(T_i), w_i)$$

$$s(t \mid \Lambda(T_i), w_i) = \exp(-\int_0^t \lambda_0(t)(\boldsymbol{\gamma}^T \mathbf{W} + U_{2i}(t))dt)$$

In general to build the joint model from a Bayesian perspective, the prior distributions for all unknown parameters must be specified and then estimation and inference is conducted based on the posterior distribution of the parameters given the data. For this study, the standard prior distribution which was aided by Rizopoulos (2014) for the JMbayes package was considered. In particular, for the vector of fixed effects of the longitudinal sub model, for the regression parameters of the survival model, for the vector of spline coefficients for the baseline hazard γ_{h0} , and for the association parameter independent univariate diffuse normal priors were assumed and for the covariance matrix of the random effects an inverse Wishart prior were assumed.

3.4.4.2. Markov chain Monte Carlo (MCMC) algorithm

When we often have very large size of number of unknown parameters to be estimated then the denominator involves integration over the size of dimensional parameter space which becomes intractable for large values of dimension of parameter spaces say more than 100 dimensions. In such cases Markov Chain Monte Carlo (MCMC) algorithm is a numerical method for evaluating such complex integrals via Monte Carlo simulation from a Markov chain that is constructed so that its stationary distribution is the posterior. The MCMC algorithm combines Monte Carlo integration and Markov Chain sampling; Monte Carlo integration is a numerical integration

method which simplifies a continuous distribution by taking discrete samples. If discrete random samples of size m from a certain density took and label $\theta^{(1)},\ldots,\theta^{(m)}$, then the values $\theta^{(s)}$ are selected based on the probability density, f (θ) , such that more samples are made where f (θ) is relatively high.

Drawing samples directly from the target density f (θ) is not always achievable because it may have a complex, or even unknown, form. Markov chains provide a method of drawing samples from target densities (regardless of their complexity). The method simplifies the sampling by breaking it into conditional steps. Using these conditional steps, a chain of samples ($\theta^{(1)}...\theta^{(m)}$) will build up after specifying a starting value$\theta^{(0)}$. The Gibbs sampler is one way of generating Markov Chain. It splits the parameters into a number of components and then updates each one in turn (Rajeeval, 2006).

3.4.5. Model selection

Different model selection criteria was considered to select an appropriate separate model as well the joint model among the different fitted models to come up with an appropriate model that appropriately represent the outcome variable.

Likelihood ratio tests: The likelihood ratio test was used to test for an adequacy of the new fitted model is nested in the previous model which is given by:

$X_{LR}^{2} = -2[\log\left(\hat{L}(1)\right) - \log(\hat{L}(2))]$ Where; $\log(\hat{L}(1)$ and $\log(\hat{L}(2))$ represents the log likely hood of previously fitted model and the new fitted model and is approximately distributed as X^2 (Li meng,1992).

Akaike's information criterion (AIC): To select an appropriate separate linear model for the linear mixed modeling of longitudinal part; linear mixed model and survival model among different fitted models their AIC values was considered and the model with minimum AIC value is considered as an appropriate model among the fitted separate models.

For the survival separate model the AIC value is given by:

$AIC = -2(\log \text{likelihood}) + 2(c + k + 1)$ Where k is the number of covariates in the model and c is the number of model-specific ancillary parameters. The addition of 2(k +c+1) can be thought of as a penalty if non predictive parameters are added to the model (Akaike,1974).

Where the AIC value for the longitudinal model is given by:

AIC = -2 log Lik + 2npar; npar denotes the number of parameters in the model.

Deviance information criteria (DIC): For the joint model selection to have an appropriate shared parameter structure that associates the two processes the DIC was considered. The recently, provided simple and intuitively appealing extension of the AIC criterion called the deviance information criterion, or DIC (by Spiegelhalter *et al.* 2002), is based on the posterior distribution of the deviance statistic as,

$$D(\theta) = -2 \log f(y|\theta) + 2 \log h(y) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (18)$$

Where $f(y|\theta)$ is the likelihood function for the observed data vector **y** given the parameter vector **θ**, and h(y) is some standardizing function of the data alone (which thus has no impact on model selection). In this approach, the fit of a model is summarized by the posterior expectation of the deviance, $\overline{D} = E_{\theta|y}[D]$, while the complexity of a model is captured by the effective number of parameters, pD. Where pD is given by:

$$pD = E_{\theta|y}[D] - D(E_{\theta|y}[\theta]) = \overline{D} - D(\overline{\theta}) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (19)$$

That is the expected deviance minus the deviance evaluated at the posterior expectations. The DIC is then defined analogously to the AIC as the expected deviance plus the effective number of parameters, i.e.

$$DIC = \overline{D} + pD \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (20)$$

Since small values of $\overline{D}$ indicate good fit while small values of pD indicate a parsimonious model, small values of the sum (DIC) indicate preferred model. As with AIC and other penalized likelihood criteria, DIC is not intended for identification of the 'correct' model, but merely as a method of comparing a collection of alternative formulations (all of which may be incorrect). The attractive aspect of DIC is that it may be readily calculated during an MCMC run by monitoring both θ and D(θ), and at the end of the run simply taking the sample mean of the simulated values of D, minus the plug-in estimate of the deviance using the sample means of the simulated values of θ.

3.4.6. Model checking and diagnosis

The model diagnostic for model checking is an essential part of the modeling process to check whether the fitted model is correct or not. Different commonly used model checking was

considered to evaluate whether the fitted model is adequate or not for the separate as well for the joint model.

3.4.6.1. Model diagnosis for longitudinal separate model

Before making inferences about a fitted linear mixed model, we will have to check whether the underlying distributional assumptions about the distributional assumption of within group error and the random effect appear valid for the data. To check whether it is valid or not the diagnostic is plot of residual with fitted value will be used for the both assumption checks.

3.4.6.2. Model diagnosis for the survival separate model

Cox-Snell residuals: The residual which is proposed by Cox and Snell (1968) is the most widely used in the analysis of survival data is the Cox-Snell residual. The Cox-Snell residual for the i[th] individual, $i = 1,2,\dots,n$, is given by Properties and features of residuals, when survival outcome are modeled, have been extensively studied in the literatures. The Cox -Snell residuals are commonly used for a direct assessment of excess events (i.e., to reveal subjects that are poorly fit by the model), and for evaluating whether the appropriate functional form for a covariate is used in the model. The cox-snell residual is given by:

$$r_i = \hat{\Lambda}_0(t_i)\exp(\mathbf{w}_i^T\hat{\boldsymbol{\gamma}}) \quad \text{..... (21)}$$

Where; $\hat{\Lambda}_0(t_i)$ is Breslow estimator of the baseline cumulative hazard function at t_i and the residuals in right censored data constituting a censored sample of the unit exponential distribution; If the residuals r_i do not follow a straight line, we know that the survival times do not have a baseline hazard function which is exponential we can say that the model is not good fit data.

Martingale residuals: Martingale residual is also used to diagnosis whether the functional form of the covariate is correct or not for the fitted model. For the i[th] individual where i=1,2,…,n the martingale residual is given by:

$$\begin{aligned} r_i^m &= \delta_i - \hat{\Lambda}(t_i) \\ &= \delta_i - \hat{\Lambda}_0(t_i)\exp(w_i\hat{\gamma}) \end{aligned} \quad \text{.....(22)}$$

Where; $\hat{\Lambda}(t_i)$ is the fitted cumulative hazard function of the survival model and by plotting the martingale residuals of covariate, we can verify for the best linearity structure of the covariates in the model (Collett, 2003).

Schoenfeld residuals: The Schoenfeld residuals is used to test for covariates used in PH model whether satisfy the proportional hazard assumption or not. From the partial likelihood, we know that the parameter $\boldsymbol{\gamma}$ are estimated from:

$\sum_{i=1}^{d}(w_i - E(w_i|R(t_i))=0$……(23)

With $E(w_i|R(t_i) = \frac{\sum_{l\in R(t_i)} \mathbf{w}_l \exp(\mathbf{w}_l{}^T\boldsymbol{\gamma})}{\sum_{l\in R(t_i)} \exp(\mathbf{w}_l{}^T\boldsymbol{\gamma})}$ and the schoenfeld residual is defined as

$r_i{}^s = w_i - E(w_i|R(t_i))$ Here we plot $r_i{}^s$ versus ranks of the survival times and view whether there is a time trend on the plot (Schoenfeld, 1982).

3.4.6.3. Diagnosis for the joint model

Diagnosis for the Convergence of MCMC samples: Making inferences using Markov chain samples is based on the assumption that the sample densities for the unknown parameters are good estimates of the target densities. Assessing chain convergence is therefore a key part of any analysis that uses Markov Chains. A simple (informal) method of assessing chain convergence is to look at the history of iterations using a time series plot. If the chains show a reasonable degree of randomness between iterations, it signifies that the Markov chain has found an area of high likelihood and is integrating over the target density and hence indicating that it has converged (MK Cowles, 1996).

4. ANALYSIS AND RESULTS

4.1. Data description

The data consists of 254 co-infected patients who were 18 years old or older and who were on ART follow up between first February 2009 and first July 2014 in JUSH. All HIV/TB co-infected patients who were below 18 years and those patients who started ART before first February 2009 or after first July 2014 are excluded for the analysis.

As mentioned in Section 3.3.1., the two response variables were considered for the study; longitudinal and survival responses. The survival end point is the death of HIV/TB co -infected patients during first February 2009 to first July 2014 and those patients who missed the follow up; transferred to another hospital between the specified time period and who are still on ART follow up on first July 2014 were considered as censoring values. Time-to-death HIV/TB co-infected patients in days were obtained subtracting date of co-infection from date of occurrence of event interest (death) where as for the censoring time was obtained by subtracting from the last visit of the co-infected patients.

Among the total co-infected patients during the time period thus 83(32.67%) were died due to HIV/TB co-infection where as 171(67.33%) were censored co-infected patients. The estimated average age of died co-infected patients were 32.72 years with standard deviation value of 9.44 years while the estimated average age of censored patients were 31.98 years with standard deviation of 8.54 years.

The demographic information and some basic base line covariate from the co-infected patients were also reported on table 2 below. As observed from the table below by the categorical group of the covariates out of total of 254 co-infected patients 139(54.80%) of them were males and 47(56.60%) death were also occurred in male groups in comparison with female co-infected patient groups. More than half 147(57.90%) of the co-infected patients belongs to orthodox religious groups were 18(6.70%) belongs to protestant religious groups of the total deaths occurred in these categories large number 49(59.00%) of deaths were occurred in orthodox religious groups were 4(4.8%) of deaths occurred in protestant religious groups when we made descriptive comparison between religious groups. When we look at the educational level category of the co-infected patient's larger number 109(42.90 %) were attended their primary education while only 17(6.70%) attended their tertiary educations.

Table 2: Frequencies and percentages for the baseline categorical covariates together with the status of co-infected patients

Variables	Categories	Total n (%)	Status of the observation	
			Censored observations n(%)	Observed events n(%)
Religion	Muslim	89(35.30)	59(34.90)	30(36.10)
	Orthodox	147(57.90)	98(57.40)	49(59.00)
	Protestant	18(6.70)	14(7.70)	4 (4.80)
Education	Not educated	58(22.60)	37(21.30)	21(25.30)
	Primary	109(42.90)	77(45.00)	32(38.60)
	Secondary	70(27.80)	45(26.70)	25(30.10)
	Tertiary	17(6.70)	12(7.10)	5(6.00)
Marital status	Divorced	21(8.30)	13(7.70)	8(9.60)
	Married	112(44.00)	81(47.30)	31(37.30)
	Separated	26(10.30)	10(5.90)	16(19.30)
	Single	74(29.00)	49(28.40)	25(30.10)
	Windowed	21(8.30)	18(10.70)	3(3.60)
Residence	Rural	37(14.30)	26(14.80)	11(13.30)
	Urban	217(85.70)	145(85.20)	72(86.70)
Soft drugs use	NO	120(47.20)	93(54.40)	27(32.50)
	YES	134(52.80)	78(45.60)	56(67.50)
Smoking	NO	192(75.80)	140(82.20)	52(62.70)
	YES	62(24.20)	31(17.80)	31(37.30)
Use of alcohol	NO	157(61.90)	116(68.00)	41(49.40)
	YES	97(38.10)	55(32.00)	42(50.60)
Working time	Not working	18(7.10)	13(7.70)	5(6.00)
	Part timer	8(3.20)	5(3.00)	3(3.60)
	Unemployed	17(63.50)	105(61.50)	56(67.50)
	Working full time	67(26.20)	48(27.80)	19(22.90)
Functional status	Ambulatory	126(49.60)	78(45.60)	48(57.80)
	Bed ridden	25(9.90)	10(5.90)	15(18.10)
	Working	103(40.50)	83(48.50)	20(24.10)
Type of TB	Extra Pulmonary	122(48.00)	83(48.50)	39(47.00)
	Pulmonary	132(52.00)	88(51.50)	44(53.00)
WHO Clinical stage	Stage I	8(3.20)	7(4.10)	1(1.20)
	Stage II	23(8.70)	19(10.70)	4(4.80)
	Stage III	124(48.80)	85(49.70)	39(47.00)
	Stage IV	99(39.30)	60(35.50)	39(47.00)
Sex	Female	115(45.20)	79(46.20)	36(43.40)
	Male	139(54.80)	92(53.80)	47(56.60)

Among the total deaths occurred in educational level category 32(38.60 %) deaths occurred in primary education level category groups while smaller number of deaths 5(6.00%) occurred in tertiary educational level group.

Among the total by marital status category 112(44.00%) of the co-infected patients were married while smaller number 21(8.30%) of the co-infected patients belong windowed marital status groups of the total deaths occurred in these groups 31(37.30 %) and 3(3.60 %) of the deaths occurred in married and windowed marital status groups in comparison with other marital status groups respectively which represents the larger and smaller percentages according to the marital status category. More of these co-infected patients 217(85.70 %) came from the urban and large number 37(86.70 %) of deaths also occurred in this group in comparison with rural areas of the town. Of the total co-infected patients only 62(24.20 %) were smokers and of the total death occurred in smoking status category 31(37.30 %) of the deaths occurred in smoker category group when we made descriptive comparison with none smoker group. Of the total co-infected patients by their base clinical stages 8(3.20 %) were at clinical stage I, 23(8.70 %) were at clinical stage II, 124(48.80 %) were at clinical stage III and the rest 99(39.30%) were at clinical Stage IV whereas of the total deaths occurred in clinical stage categories 39(47.00%) deaths were occurred in both clinical stage III and IV at base line time in comparison with remaining baseline clinical stages. There were 103(40.50%) patients who were able to work; 126(49.60%) were ambulatory and 25(9.90 %) were bedridden in the functional status categories; of the total patients deaths in these categories 48(57.80 %) of the deaths were occurred in patient group who was ambulatory at the base line during the co-infection time.

The longitudinal response was the number of CD4 cells counts per mm^3 of blood which were measured approximately every 6 months from date of co- infection at the base line time to end of the study period. Since the CD4 is the count measurement we transformed to continuous measurement by using square root transformation to be analyzed as the continues response and the normality of the transformed value was checked by using box plot of figure 5 on annexes part.

Without considering the censoring status of the HIV/TB co-infected patients the average number of square root of CD4 count measurement with their standard deviation at each time point was reported on the table 3 below. As it can be observed from table 3 the mean square root of CD4

count measurement is (11.91) at base line; it have an increasing value from baseline up to 30 months and it has declining value after 30 months. When we look at the standard deviation of the mean value of square root of CD4 count measurement between baseline times up to 36 months there was no much variation between square root of CD4 count measurement and after 36 months the standard deviation values have decreasing value.

Table 3: Mean of square CD4 count measurement with its standard deviation at each time points with respective of the sample sizes.

Time points in month	0	6	12	18	24	30	36	42	48
Sample size	254	156	134	105	65	43	23	9	3
Mean square root of CD4	11.91	16.10	18.09	19.42	19.39	19.84	18.88	16.78	14.82
Standard deviation	5.37	5.31	4.85	5.00	5.15	5.50	5.29	3.65	1.18

With considering the censoring status of co-infected patients the mean and standard deviation square root of CD4 count measurement and the weight of censored and died co-infected patients at each time points were given as follows on table 4 below.

Table 4: Mean of square root of CD4 count measurement and weight with their standard deviation at each time points for died and censored co-infected patients.

	For censored observation				For the observed events			
Time points(in month)	Square root of CD4		Weight		Square root of CD4		Weight	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Stand deviation
0	12.57	5.21	49.58	10.96	10.62	5.42	45.93	9.59
6	16.45	5.05	53.52	11.45	14.29	6.26	50.69	7.71
12	18.27	4.85	55.65	10.02	17.58	4.66	51.56	6.96
18	19.62	5.04	56.54	10.24	18.24	4.98	50.67	7.55
24	19.45	5.33	58.32	11.19	18.91	3.22	46.63	3.46
30	20.63	5.61	59.31	10.99	19.79	5.24	49.38	7.07
36	18.69	5.60	57.35	8.92	20.18	2.71	51.67	4.73
42	17.15	3.34	60.13	11.96	19.82	2.98	46.53	5.32
48	14.82	1.18	64.33	13.61	-	-	-	-

As reported on table 4 above in all time points the square root mean of CD4 count measurement of censored co-infected patients from base line time to 30 months is larger than that of died co-infected patients where as there was no big difference in standard deviation of square root of

CD4 count measurement in censored co-infected patients from base line time up to 36 months in comparison with died co-infected patients. When we look at the mean weight in all time points the mean weight of censored co-infected patients have larger weight than died co-infected patients where as the variation in weight of died co-infected patients was lower than that of censored co-infected patients.

4.2. Results using separate models

We initially analyzed data separately using both longitudinal and survival models described in Section 3.4.1 and 3.4.2. This is important for the fully specification of the mean response of the model and determine the random effects and fixed effects to be included in the longitudinal sub-model, and to indentify the covariates that have a contribution for the hazard of an event in the survival sub-model to provide initial values for the joint analysis.

4.2.1. Separate analysis of the longitudinal data

In any data analysis, before directly going to the analysis first the data exploration were employed for the longitudinally measured CD4 count measurement of HIV/TB co-infected patients.

4.2.1.1. Exploring individual profile and the mean structure

Data exploration is a very important tool to fit of appropriate models and to look at pattern of data over time. It show as much of the raw data as possible rather than summarized values, highlight aggregate patterns of scientific interest.

The individual profile plot of figure 1 below indicates within and between subjects variability square root of CD4 count measurement of HIV/TB co-infected patients where as the loess smoothing technique suggest the linear and quadratic growth effect in the mean structure of square root CD4 count measurement over time.

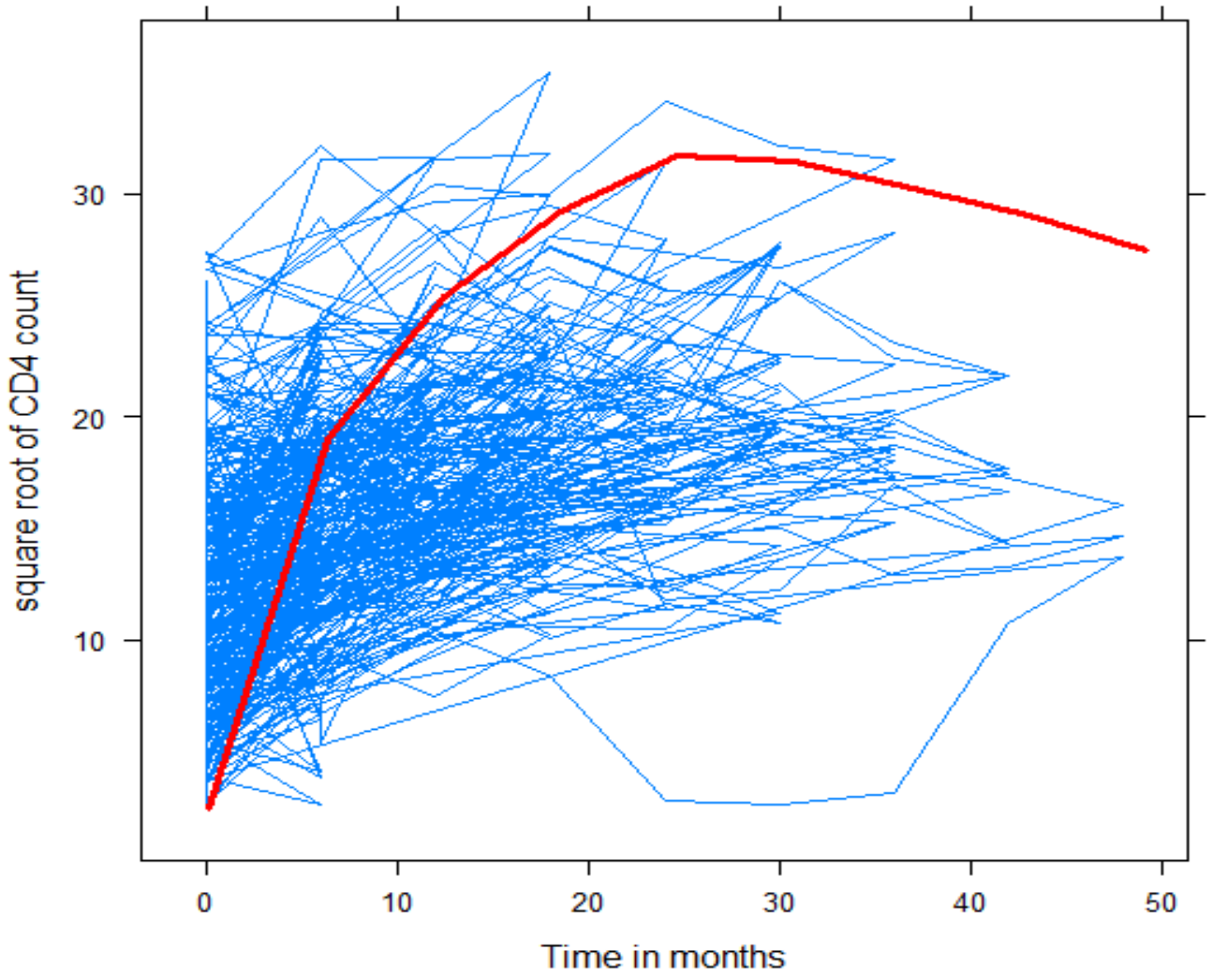

Figure1: Individual profile plot with loess smoothing technique

Exploring the Mean Structure: To understand the possible relationships among the CD4 means over time, a plot of a line connecting the average values computed at each time point is shown below on Figure 2 The mean structure plot suggests that the mean of the square root CD4 profiles have a non linear growth over time which looks quadratic relationship over time. Since the data is not balanced loess smoothing technique is an appropriate to suggest the mean structure also since it local weighted least square (loess) smoothing curve of the individual profile plot also suggests the linear and quadratic effect mean structure; therefore both the linear and quadratic time effects was included as fixed-effects in the model.

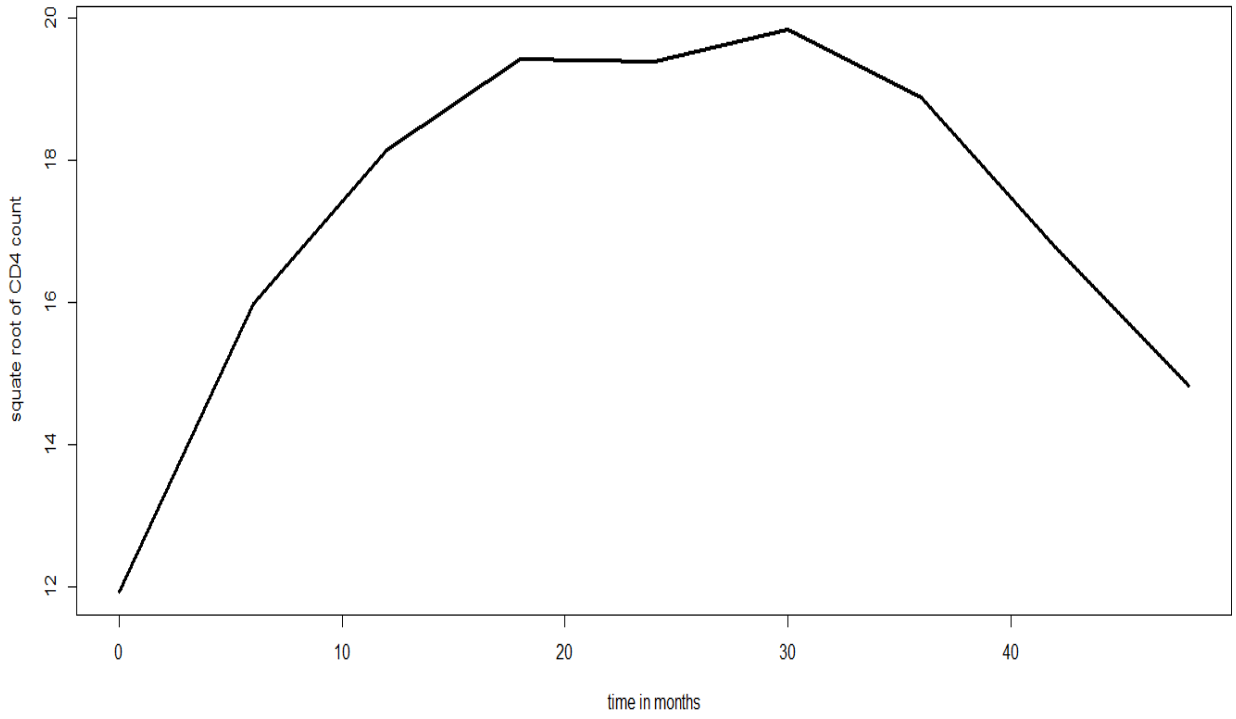

Figure 2: The mean of square root of CD4 count measurement evolution structure over time

4.2.1.2. Linear mixed effects models results

From the individual profile and mean structure exploratory analysis, both linear and quadratic age effects seem to be useful in modeling the random effects. Therefore as described under methodology the linear mixed model was built within two stages in which the first stage involves fitting linear regression model which only considers between subjects variability and selection of an appropriate fixed effect for the outcome variable based on the likelihood ratio test and AIC values of the fitted candidate linear models. Therefore let Y_{ij} is the measured square root of CD4 count measurement measured for the co-infected patients at time t_{ij} ,i=1,2,…,N, j=1,2,…,n_i the selected an appropriate linear model among different fitted candidate model using model selection criteria was specified as:

$$Y_i = \beta_0 + \beta_1 time + \beta_2 time^2 + \beta_3 c.stageIII + \beta_4 c.stageIV + \beta_5 alcohol + \beta_6 working + \beta_6 bedridden + \beta_7 weight + \beta_8 time * c.stageIII + \beta_9 time * c.stageIV + \beta_{10} time * alcohol + \beta_{11} time * working + \beta_{12} time * bedridden \beta_{13} time * weight + \beta_{14} time^2 * working + \beta_{15} time^2 * bedridden + \beta_{16} time^2 * weight + \varepsilon_i$$

…….. …… (4.1)

where;

$Y_i = (Y_{i1}, Y_{i2}, \ldots, Y_{ini})$ and $\varepsilon_i \sim N(0, \Sigma_i)$

The model (7) specified above only accounts the observed variability between subjects and the covariates of the model was selected from table 1 of methodology parts based on model information criteria of the fitted models that appropriately explain the square root of CD4 count measurements by accounting only the between variability of the co-infected patients.

The summary of fitted model (7) reported on table 5 below showed that clinical stages; use of alcohols; bed ridden functional status and quadratic time effect have negative effects where as linear time effect and working functional status have positive effects on square root of CD4 count measurement at 5% significance level. When look at the interaction effect of covariates with linear time effect clinical stage IV have positive effect where weight and working functional status have negative effects on the CD4 count measurement of HIV/TB co-infected patients. The interaction effects of weight and working functional status with quadratic time effects have positive effects on square root of CD4 count measurement at 5% significance level where the remaining covariates interacting with linear time and quadratic time have no significant effect on square root of CD4 count measurement HIV/TB co-infected patients case of JUSH at 5% significance level since their 95% confidence intervals of these covariates includes zero. The estimated intercept value indicates that the mean base line CD4 count measurement was 12.68 cells per mm^3 without effects of other covariates further more CD4 count measurement was differ by WHO clinical stages; functional status and use of alcohol when only the between subject variation is considered.

The constant variance and normality assumption diagnosis of the fitted linear model was checked by using residual versus fitted value and quantile-quantile plots figure 6 and 7 on the annexes of the error terms respectively and the plots showed with exception of some outliers there was no problems of the assumptions.

Table 5: Linear model selected for the fixed effects with 95% confidence interval of the estimated coefficients

Covariates	Estimated coeff ($\hat{\beta}$)	95 % CIs
Intercept	12.6819	[9.6794,15.6844]*
Time	1.1305	[0.6482,1.6128]*
Clinical stage		
Stage III	-1.6036	[-3.1251,-0.0820]*
Stage IV	-1.5755	[-3.1409,-0.0101]*
Alcohol user	-0.9127	[-1.9703,-0.0009]*
Functional status		
Bedridden	-2.9229	[-4.9498,-0.8961]*
Working	2.6039	[1.3759,3.8318]*
Weight	0.0079	[-0.0452,0.0609]
Time^2	-0.0303	[-0.0459,-0.0146]*
Time*stage III	0.0776	[-0.0143,0.1696]
Time*stage IV	0.1573	[0.0604,0.2541]*
Time*alcohol user	0.0152	[-0.0591,0.0895]
Time:Bed ridden	-0.2259	[-0.6801,0.2282]*
Time:Working	-0.2336	[-0.4185,-0.0487]*
Time*Weight	-0.0094	[-0.0175,-0.0012]*
Weight:Time^2	0.0003	[0.00003,0.0005]*
Bed ridden:Time^2	0.0034	[-0.0125,0.0194]*
Working:Time^2	0.0055	[0.00004,0.0111]*
$\hat{\delta}_{\varepsilon}$ =4.933		AIC=4795.4070

*Indicates the significance of covariates at 5% level of significance

The linear mixed model is the sum the selected fitted fixed effects and the random effects; it accounts both within and between subject sources of variations. To have an appropriate linear mixed model the selected fixed effects were fitted with different random effects starting with only random intercept up to random intercept; linear and quadratic slopes. Indeed; the final appropriate linear mixed model was selected based on the AIC and BIC of the fitted models and the linear mixed model with minimum information criteria is considered as an appropriate one

according to the AIC and BIC model selection criteria. The specified linear mixed model to be fitted is given as:

$\mathbf{y}_{ij} = \mathbf{X}^T\boldsymbol{\beta} + \mathbf{U}_{1i}(t_{ij}) + \boldsymbol{\varepsilon}_{ij}$, $\mathbf{X}^T\boldsymbol{\beta}$ is the fixed effect estimated in linear model above where as

$U_{1i}(t_{ij}) = b_{0i} + b_{1i} * Time_{ij} + b_{2i} * Time^2{}_{ij}$ .Here, $U_{1i}(t_{ij})$ includes the random effects for intercept, linear and quadratic time slopes, where $\mathbf{b_i}=(b_{0i},b_{1i},b_{2i})^T \sim N(\mathbf{0},\mathbf{D})$ they allows different subjects to have different baseline CD4 counts, different linear and quadratic time trends for CD4 counts during the ART follow up periods. The summaries of fitted different LMM by considering different random effects were reported on the table 6 below.

Table 6: AIC and BIC value of the fitted linear mixed effects model by considering different random effects

Random effects	AIC	BIC
Random intercept	4593.5800	4686.6115
Random linear slope	4790.3252	4883.3560
Random intercept and linear slope	4579.8185	4682.1531
Random quadratic slope only	4855.5364	4948.5673
Random intercept and quadratic slope	4596.1601	4698.4950
Random linear and quadratic slopes	4738.0072	4840.3416
Random intercept; linear and quadratic slope	4545.2743	4661.5631

As reported on table 6 above to have an appropriate linear mixed model for the longitudinal model the selected fixed effect model or the selected linear model was fitted with different random effects as observed from table 6 seven linear mixed models were fitted with different random effects starting from random intercept to random intercept; linear and quadratic time slopes. Of the seven fitted LMM the model fitted with random linear and quadratic slope only have larger AIC and BIC values and we consider these LMM as worst models when compared to the remaining LMM models but when we add intercept to these random effects there is an improvement of the model since the adding of subject specific intercept to the random linear and quadratic time effect slopes there was an improvement of the LMM since there was the reduction of AIC and BIC values. Finally we reach on an appropriate LMM which have minimum AIC and BIC values that is 4545.2743 and 4661.5631 respectively which was obtained by fitting the selected fixed effects with adding subject specific intercept; linear and quadratic slopes of time

random effects. After the appropriate random effect was selected for LMM an appropriate covariates was selected among the selected fixed effects of the fitted linear model for the optimality of the linear mixed model. The final fitted an appropriate linear mixed model for the longitudinal separate model was reported on the table 7 below.

As we can easily observe on reported table 7 after accounting within subject variability of co-infected patients for the CD4 count measurements at different time points; at base line the CD4 count measurement of working functional status groups were 2.633 greater and bedridden functional status groups were 3.174 lower CD4 count measurements in comparison with ambulatory functional status groups. The estimated coefficient weight 0.063204454 shows that positive effect of weight on CD4 count measurement which indicates with unit change in weight of HIV/TB co-infected patients increases their mean square root of CD4 count measurement by 0.063204454 holding other covariates constant. When we look at the mean evolution of CD4 count measurements co-infected patients ; working functional status interacting with linear time effect have negative effect were as interacting with quadratic effect have positive significant effect at 5% level significance on square root CD4 count measurement of co-infected patients.

When we look at the time effect on the reported table linear time effect have positive effect were as quadratic time effect have negative effect on CD4 count measurements furthermore the mean square root of CD4 count measurement at base line was 8.64 without the effects of covariates.

The two within and between subject variations assumptions of the linear mixed model were checked by using the graphical plots of figure 8 and 9 on annexes for between subject variation assumption and figure 10 and 11 on annexes for the within subject variation assumption and the plots showed with exception of some outlying values there was no problems of the assumptions and the fitted model is good fit the data.

Table 7: The final selected linear mixed model estimated parameter with their 95% confidence interval

Fixed effects	Estimated coeff ($\hat{\beta}$)	95% CIs
Intercept	8.6409	[6.5098,10.7719]*
Time	0.6368	[0.5272,0.7465]*
Functional status		
Bed ridden	-3.1745	[-5.3001,-1.0489]*
Working	2.6337	[1.3308,3.9366]*
Alcohol user	-0.7797	[-1.9352,0.3759]
Weight	0.0632	[0.0212,0.1052]*
Time^2	-0.0121	[-0.0148,-0.0095]*
Time: Bed ridden	-0.1068	[-0.4668,0.2532]
Time: Working	-0.2597	[-0.4089,-0.1104]*
Bed ridden: Time^2	0.00467	[-0.0057,0.0150]
Working: Time^2	0.0059	[0.0023,0.0095]*
Random effects		
$\hat{\delta}_{b_0}$	4.2594	[3.7849,4.79343]
$\hat{\delta}_{b_1}$	0.3404	[0.2746,0.422]
$\hat{\delta}_{b_2}$	0.0064	[0.0048,0.0086]
Between subject error		
$\hat{\delta}_{\varepsilon}$	2.6271	[2.4421,2.8261]
	AIC =	4497.6390

*Indicates the significance of covariate at 5% level of significance

4.2.2. Separate survival data analysis

4.2.2.1. Kaplan-Meier survival function estimates

The Kaplan-Meier estimator is applied to estimate the survival curves for categorical covariates. The Kaplan Meir estimated median value that the half of the patients experience the event was 62.5 months. The Kaplan Meir was also used to estimate the survival probability for the category of the covariates and the estimated survival probability curve of some selected categorical covariates; is displayed on figure 3 and 4 as follow:

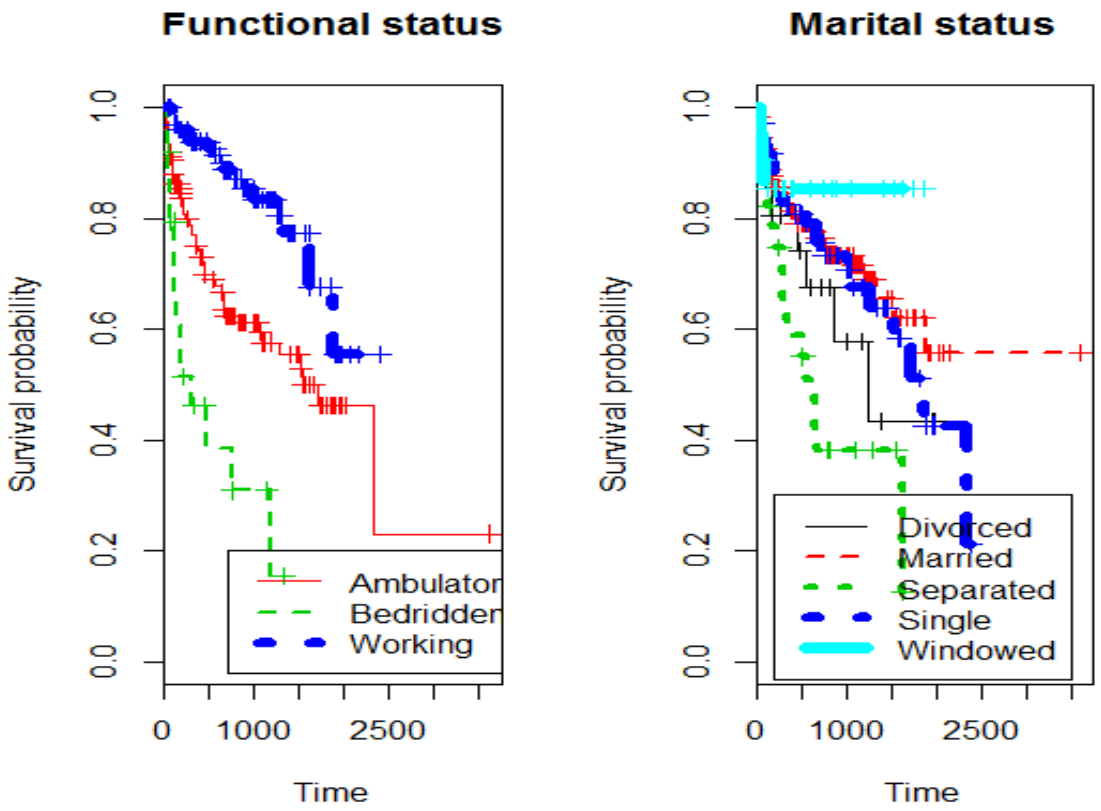

Figure 3: Estimated Kaplan-Meier survival curve for marital status and functional Status

As can be observed from the plot the left hand figure shows that survival curve by functional status of co-infected patients. Those patients who are working at the base line have higher survival time than co-infected patients those who were either ambulatory or bed ridden at base line time whereas who were bedridden at the base line have lower survival probability than those who were either ambulatory or working at base line time.

The right hand side of the plot of figure 3 above indicates the survival probability curve by marital status indicating that except for windowed marital status group married co-infected patients have higher survival probability curve than divorced; separated and single marital status groups where as with exception of sometime points for divorced individuals co-infected patients who were belongs to separated marital status group have lower survival probability curve than the remaining marital status groups.

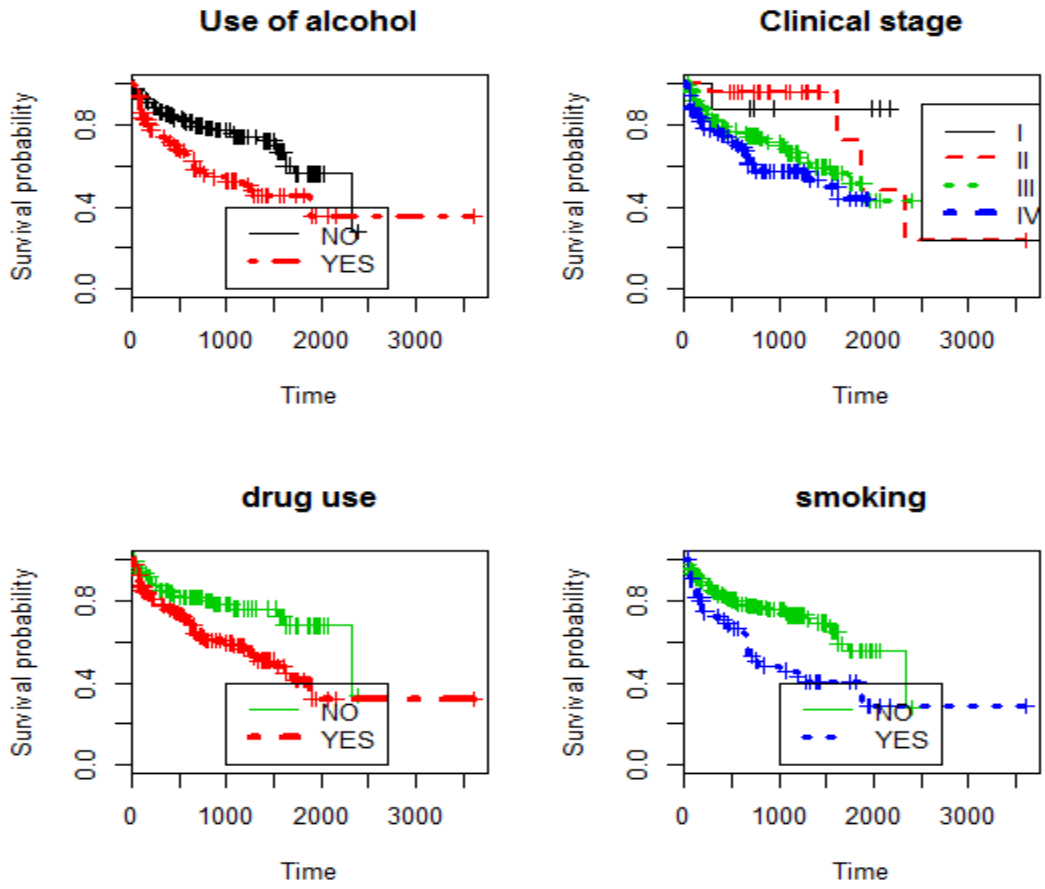

Figure 4: Estimated Kaplan-Meier survival curve use of alcohol; WHO clinical stage; use of drug and smoking status of co-infected patients.

As shown the plots of figure 4 above the upper left corner plot the survival probability curve of co-infected patients who did not use alcohol have higher probability curve than alcohol users up to time period between 2500 days and 200 days. The upper right corner plot shows co-infected patients who were at clinical stage IV at base line have lower survival probability curve than the remaining clinical stage groups. The bottom left corner plot indicated the co-infected patients who did not use soft drugs specially chat have higher probability curve than the soft drug users up to time of near 2500 days. The bottom right plot also showed non smokers have higher survival probability curve than smoker co infected patients at base line.

To test the significance difference of the plotted curves by different covariates the log rang tested were employed and the result of log rank test was reported as follows on table 8 below.

Table 8: Log rank tests of survival curve differences for categorical covariates

Covariates	Chi-square	DF	Pr>chi-square
Sex	0.2000	1	0.6750
Functional status	37.5000	2	7.08E-09
Type of TB	0.1000	1	0.7150
WHO clinical stage	10.4000	3	0.0153
Religion	0.3000	2	0.8530
Educational level	2.3000	3	0.5120
Marital status	14.3000	4	0.0063
Residence	0.0050	1	0.8450
Drug	9.8000	1	0.0017
Smoke	10.7000	1	0.0011
Alcohol	8.9000	1	0.0028
Working time	0.7000	3	0.8710

As indicated on log rank test of each covariate on table 8 above there was a significance difference in survival probability curve by functional status; WHO clinical stage; marital status; use of drug; smoking status and use of alcohol groups co-infected patients since the computed P-value of log rank test statistics for these covariates were less than 5% significance level where as there was no significance difference in survival probability curve by sex; type of TB; religion; educational level ;residence and working time groups of co-infected patients since the p-value of the computed log rank test statistics for these covariate groups were greater than 5% significance level.

4.2.2.2. Survival models and variable selection for the model

To determine the variables to be included in the survival model, an automatic variable selection method stepAIC in R were used. Regardless of the survival time distributions, among all covariates used for the study and smoking status; base line weight; functional status; type of TB; WHO clinical stage and marital status were extracted to be included in the model.

In order to select the appropriate survival time model among the most commonly used parametric models; the Weibull, Exponential, Log logistic and Lognormal models and semi-parametric (Cox PH) model the AIC values and graphical methods figure 13 of the annexes

were used to make compare among the parametric survival model that is the function of estimated Kaplan Meir probability plot versus the function of time plot meaning log of KM versus time plot for exponential; log(-log(KM)) versus log time plot for Weibull; log(KM/(1-KM)) versus log of time for log logistic and qnorm(1-KM) versus log time plot for the log normal distributions for the linearity structure; to identify the parametric model that appropriately represent the linearity structure for the survival time and we have identified among the four parametric distributions the Weibull parametric model since the plotted figure of log(-log(KM)) versus log time looks linear fit than for the remaining parametric distribution plots. We also made comparison among the fitted survival models using AIC values of the models which was reported on the table 9 below to have an appropriate model for the separate survival model.

Table 9: AIC and log likelihood values for the fitted null and full survival models

Survival model	Null model		Full model	
	Log likelihood	AIC	log likelihood	AIC
Cox PH	-408.9211	817.8418	372.5981	769.1962
Weibull	-723.3663	1450.7310	-685.6893	1398.3770
Log normal	-724.5754	1451.1492	-686.1967	1400.3925
Exponential	-728.0028	1458.0045	-686.2761	1399.5534
Log-logistic	-723.8480	1450.8961	-686.4150	1400.8301

As reported on the table 9 above, since the models are not nested, it is not possible to compare the models using log-likelihood values. When the AIC values were used to make comparison among the parametric survival models; among the fitted parametric survival models using AIC values for the full model among the parametric survival models their AIC values looks near to each other and the Weibull survival model have minimum AIC values in comparison with the remaining parametric survival models which also confirms the graphical methods of comparison since the graphical method also suggested Weibull parametric models on average looks linear fit than the remaining parametric models. Therefore; we prefer the Weibull parametric survival model among the parametric survival models.

To have Weibull model as final an appropriate survival model we should have to also compare with that of semi parametric model whether it is better fit than the semi parametric model or not. Making comparison using AIC values of parametric model with that of semi parametric survival model is not enough since the parametric survival model was based on the full likelihood function where as the semi parametric survival model was based on the partial likelihood functions when we look the estimated survival probability curve at base line of the figure 14 of annexes part with both models the estimated probability curves by the two methods looking over lapping at some time points and the estimated probability curve by the Weibull was larger at some time points. Even if it is not perfectly correct to make comparison of semi parametric with the parametric model using their AIC values of when the AIC values the Weibull survival model looks worse than the Cox PH model since its AIC value1399.3770 was very bigger than that of Cox PH AIC model value 769.1962. Indeed; since the AIC value of Cox PH model was quite very smaller than of the Weibull parametric survival estimates and the estimated survival probability curve also looks the Cox PH estimates the survival probability than that of the Weibull parametric model. Therefore; we prefer Cox PH model than Weibull parametric survival model to model the separate survival time of HIV/TB co-infected patients in the study area.

4.2.2.3. Cox and Weibull PH survival model results

After preferred the Cox PH model to fit the separate survival model of HIV/TB co-infected patients the estimated parameters for the Cox and Weibull PH model is presented on table 10 below. Because none of the covariates are time-varying, the specified proportional hazard model was:

$$\lambda(t/X) = \lambda_0(t)\exp(\gamma_1 stage_2 + \gamma_2 stage_3 + \gamma_3 stage_4 + \gamma_4 TBtype + \gamma_5 weight + \gamma_6 bedridden + \gamma_7 working$$
$$\gamma_8 smoking + \gamma_9 married + \gamma_{10} separated + \gamma_{11}\sin gle).....(4.2)$$

Where; $\lambda_0(t)$ was the baseline hazard which was unspecified and treated as nuisance parametric for the Cox PH model where as it was modeled parametrically for the Weibull PH the modeled base line hazard for the Weibull PH was given by $\lambda_0(t) = 0.0014 * 0.9074t^{-0.0926}$ and this represents the estimated base line hazard for the Weibull PH of HIV/TB co-infected patients. Where the estimated parameters of the Weibull PH was obtained from the accelerated failure time model of the Weibull using the relation between the accelerated failure time model and proportional hazard model which is given by:

$\hat{\lambda} = \exp(-\frac{\hat{\gamma}_0}{scale}), \hat{\alpha} = \frac{1}{scale}$ and $\hat{\gamma} = -\frac{\hat{\gamma}_{AFT}}{scale}$ where their standard error of the estimated parameters was obtained by using delta methods for the construction of the 95% confidence interval which was obtained by $\hat{\gamma} \pm 1.96se(\hat{\gamma})$ for the coefficients of the covariates. As reported on table 10 below; it is easily observed that smoking; base line weight; functional status and marital status have a significant effect on the hazard function where as the base line clinical stage status have no significant effect on hazard function at 5% significance level. As observe from the estimated parameters for both model there was no big difference between estimated values by the two models.

Table 10: The estimated parameters for Cox and Weibull PH models with their 95% confidence intervals

Covariates	Cox PH		Weibull PH	
	Estimated values	95 % CIs	Estimated value	95 % CIs
Clinical stages				
stage II	0.3042	[-1.9743,2.5827]	0.3261	[-1.9013,2.5534]
stage III	1.0891	[-0.931847,3.1099]	0.9759	[-1.0370,2.9889]
Stage IV	1.7188	[-0.3434,3.7811]	1.6337	[-0.4284,3.6959]
Pulmonary TB	0.5713	[-0.0845,1.2271]	0.5849	[-0.0829,1.2530]
weight	-0.0411	[-0.0662, -0.0160]*	-0.0423	[-0.0671,-0.0174]*
Functional status				
Bed ridden	0.6804	[0.0319,1.3289]*	0.7090	[0.06459,1.3534]*
working	-0.9296	[-1.4898,-0.3694]*	-0.9660	[-1.5375,-0.3945]*
smoker	0.7792	[0.2617,1.2966]*	0.8061	[0.2722,1.3399]*
Marital status				
married	0.1360	[-0.7131,0.9852]	0.1016	[-0.7480,0.9512]
separated	0.9842	[0.0889,1.8795]*	0.9495	[0.0471,1.8520]*
single	-0.1930	[-1.0432,0.6571]	-0.2684	[-1.1134,0.5766]
windowed	-1.1145	[-2.5252,0.2961]	-1.2265	[-2.6389,0.1859]
Lambda			0.0014	[0.00012, 0.015]
Alpha		-	0.9074	

*Indicates the significance of the covariates at 5% level of significance.

As observed from table above the base line weight, working functional status groups in comparison with ambulatory functional status groups have negative effect at 5% significant level that is they reduce hazard function of survival time where as bed ridden functional status in comparison with ambulatory; smokers groups in comparison with none smoker groups and

separate marital status groups in comparison with divorced marital status groups have positive effect on survival hazard function that is these groups are more likely to die from co-infection than their comparative groups during the co-infection period. The estimated shape parameter for the Weibull =0.9074 which is less than one shows that the death rate from co-infection was decreasing over time.

The goodness of fit was tested by using Cox-Snell residual versus cumulative hazard function plot of figure on 15 on annexes and the plot showed the beginning the fit looks strait and cuts approximately at 45^0 when we go to up the fitted looks not strait as that of begging but there is no much severity about the goodness of the fitted Cox PH model. For the linearity structure diagnosis the martingale residual plots figure 16 on the annexes showed there was no alarming linearity problem of the fitted covariates and the proportional hazard assumptions were also tested using the Schoenfield residual plots of figure 17 and 18 annexes part showed there was no failure of the PH assumption for the fitted covariates since there was no systematic departure of the residuals on the plots. In addition to the Schoenfield residual for the PH assumption numerical test are also employed and annexed on table 14 and the result showed none of the covariates are non significant at 5% significance level which supports no failure in the PH assumptions of the covariates used in the Cox PH model.

4.3. Results using joint models

Several joint models using different shared parameter association structure with different combinations of the random effect processes were explored. In all cases, the results are based on single MCMC sampling chains of 75,000 iterations each, following a 35,000 iteration "burn-in" period. The appropriate association structure was selected based on DIC values of the joint models which were reported on table 11 below.

As reported on table 11 pD and DIC scores for twenty one joint models with different random effects and different shared parameter association structure $\mathbf{U}_{1i}(t_{ij})$ and $\mathbf{U}_{2i}(t)$ respectively was described as follows. It can be easily observed that the joint models I-III were those fitted with random intercept only excluding random linear and quadratic slopes of the longitudinal sub model with shared parameter structure for the survival sub model of current value of longitudinal trajectories; the sum of fixed corresponds to random intercept and random intercept and random intercept only of these three joint models the joint model fitted with sharing random

intercept only have minimum values of pD score 285.3474 and DIC scores 7237.1170 when compared to the remaining two models and we consider this model an appropriately fit the data when the longitudinal sub model was fitted with random intercept only.

Table 11: Joint model Selection for a variety of candidate joint models when the linear mixed model and the selected Cox PH model used for the survival sub-model modeled jointly using different shared parameter structures.

Model	$U_{1i}(t_{ij})$	$U_{2i}(t)$	PD	DIC
Random intercept only				
I	b_{0i}	$\alpha\, m_i(t)$	286.1910	7243.8840
II	b_{0i}	$\alpha_0 b_{0i}$	285.3474	7237.1170
III	b_{0i}	$\alpha_0(b_{0i}+\beta_0)$	286.1823	7238.7310
Random intercept and linear slope				
IV	$b_{0i}+b_{1i}t_{ij}$	$\alpha\ m_i(t)$	527.0579	7669.0230
V	$b_{0i}+b_{1i}t_{ij}$	$\alpha_0 b_{0i}+\alpha_1 b_{1i}$	523.4795	7653.3280
VI	$b_{0i}+b_{1i}t_{ij}$	$\alpha_0(b_{0i}+\beta_0)+\alpha_1(\beta_1+b_{1i})$	525.6622	7667.8695
Random linear slope				
VII	$b_{1i}t_{ij}$	$\alpha\ m_i(t)$	741.5371	9998.8562
VIII	$b_{1i}t_{ij}$	$\alpha_1 b_{1i}$	718.3055	9821.5132
IX	$b_{1i}t_{ij}$	$\alpha_1(\beta_1+b_{1i})$	740.2094	9995.5371
Random quadratic slope				
X	$b_{2i}t_{ij}^2$	$\alpha\ m_i(t)$	280.6913	7898.5682
XI	$b_{2i}t_{ij}^2$	$\alpha_2\ b_{2i}$	273.4905	7779.8073
XII	$b_{2i}t_{ij}^2$	$\alpha_2\ (\beta_2+b_{2i})$	276.3944	7892.6497
Random intercept and quadratic slope				
XIII	$b_{0i}+b_{2i}t_{ij}^2$	$\alpha\ m_i(t)$	501.7567	9596.7041
XIV	$b_{0i}+b_{2i}t_{ij}^2$	$\alpha_0 b_{0i}+\alpha_2 b_{2i}$	503.4964	9262.5980
XV	$b_{0i}+b_{2i}t_{ij}^2$	$\alpha_0(\beta_0+b_{0i})+\alpha_2(\beta_2+b_{2i})$	458.74191	9797.7322
Random linear and quadratic slope				
XVI	$b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha\ m_i(t)$	566.1641	10247.2421
XVII	$b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha_1 b_{1i}+\alpha_2+b_{2i}$	500.9278	9585.0610
XVIII	$b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha_1(\beta_1+b_{1i})+\alpha_2(\beta_2+b_{2i})$	501.7567	9596.7046
Random intercept; linear and quadratic slope				
XIX	$b_{0i}+ b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha\ m_i(t)$	282.1523	6437.9382
XX	$b_{0i}+ b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha_0 b_{0i}+ \alpha_1 b_{1i}+\alpha_2 b_{2i}$	268.0893	6333.7416
XXI	$b_{0i}+ b_{1i}t_{ij}+b_{2i}t_{ij}^2$	$\alpha_0(b_{0i}+\beta_0)+ \alpha_1(\beta_1+b_{1i})+\alpha_2(\beta_2+b_{2i})$	271.6129	6347.1127

When the linear random slope was added to the random intercept for the longitudinal sub model and fitted with different shared parameter association structure for the joint modeling there was no improvement of the joint models for all association structures of models IV-VI since none of the joint models have lower DIC values than the models fitted with random intercept for the longitudinal sub model. When we excluded the random intercept allows only linear random slope of the longitudinal part and fitted with the three different shared parameter association structures in models VII-IX in all the three models there was no improvement of models since the DIC scores of these three models is larger than models I-III and IV-VI but when we made comparison among these three joint models the joint model sharing random linear slope association structure have a minimum DIC score 9821.5132 was appropriate fit than the remaining two joint models.

Of the joint models fitted with the random quadratic slope by excluding the random intercept and linear slope for the longitudinal sub model for models X-XII here also the joint model sharing the random quadratic slope only for the survival part was an appropriate fit than the remaining two joint models since its DIC score 7779.8073 was smaller. When we look at these joint models for the improvement of the model by including random intercepts and random slopes separately to the quadratic random effect of the longitudinal sub model or model XIII-XV and model XVII-XVIII with the three different shared parameter association structures for the survival sub model there was no improvement of the joint model since all of their DIC score values were larger than the remaining joint models.

Furthermore; we made comparison between model with linear and quadratic random slopes or model XVIII and XIV with that of with random intercept and quadratic random slope or models XVI and XVII which shares current value of CD4 count trajectories with same time period and random effect parts respectively to the survival sub-model inclusion of random intercept rather than random linear slope to the quadratic random effect for the longitudinal sub-model for the joint modeling looks appropriate fit data since they have smaller DIC values where as for models sharing random and fixed effects corresponding to the random effects of the longitudinal sub model the joint model fitted with linear and quadratic slopes model XVIII was appropriate fit than the model fitted with random intercept and quadratic slope model XV since model XVIII have lower DIC score than model XV.

Finally when we look at final fitted joint model groups which was fitted with random intercept; linear and quadratic slopes for the longitudinal sub model associated different shared parameter association structure for the survival sub model XIX-XXI there was an improvement of the joint model since the DIC score of all models of these group was smaller than all the joint models discussed before. When we made comparison among these joint model groups using their DIC score the model XX which was fitted which associates the two processes using shared random effect parameters association structure since the DIC score 6333.7416 of this model is less the remaining all joint models; we considered this model as an appropriate joint model that appropriately relates the longitudinally measured square root of CD4 count measurement process with time to death process of HIV/TB co-infected patients.

Table 12: The appropriate estimated joint model of the longitudinal measured CD4 process and Time-to- death process of HIV/TB co-infected patients

Longitudinal sub-model			Survival sub-model		
Fixed effects	Coeff ($\hat{\boldsymbol{\beta}}$)	95% CIs	Covariates	Coeff ($\hat{\boldsymbol{\gamma}}$)	95%CIs
			Clinical Stage		
Intercept	8.2361	[5.5629,10.3488]*	Stage II	1.4028	[-1.1811,4.9870]
Time	0.2876	[0.0796,0.5359]*	Stage III	1.8983	[-0.6012,5.6984]
Functional status			Stage IV	2.7416	[0.4152,6.4328]*
Bed ridden	-3.3381	[-5.4612,-1.3134]*	Pulmonary TB	0.4056	[-0.5891,1.3052]
Working	2.6762	[1.3518,3.9612]*	Weight	-0.0646	[-0.1120,-0.029)*
Alcohol user	-0.6433	[-1.8466,0.5919]	Functional status		
			Bed ridden	1.1505	[-0.2126,2.4391]
Weight	0.0729	[0.027,0.1312]*	Working	-1.3272	[-2.6340,0.0231]
Time^2	-0.0092	[-0.0126,-0.0059]*	Smoker	1.3081	[0.3391,2.1127]*
Time:Bed ridden	-0.1620	[-0.6343,0.3379]	Marital status		
Time:Working	-0.1402	[-0.5543,0.1716]	Married	-0.1798	[-1.5011,1.1710]
Bed ridden:Time^2	0.0018	[-0.0112,0.0159]	Separated	1.0548	[-0.2371,2.4592]
Working:Time^2	0.0064	[0.002,0.0108]*	Single	-0.5006	[-1.9231,0.8192]
Random effects			Windowed	-2.3774	[-5.1561,-0.097]*
$\mathrm{Var}(\hat{b}_0)$	19.1012	[15.1472,23.7416]	Association parameters		
$\mathrm{Var}(\hat{b}_1)$	33.5455	[25.4856, 41.6053]	$\hat{\alpha}_0$	-0.0585	[-0.061,-0.0566]*
$\mathrm{Var}(\hat{b}_2)$	1.4388	[1.1504,1.7994]	$\hat{\alpha}_1$	-1.798	[-1.825,-1.7561]*
$\hat{\delta}_{\varepsilon}$	2.4041	[2.1914,2.6335]	$\hat{\alpha}_2$	0.2788	[0.2114,0.332]*

*Indicates significance of the covariates at 5% level of significance

As observed from the appropriate selected joint model which has a minimum DIC score values than the remaining joint models. The longitudinal sub-model specification was the same to that of the selected linear mixed model where as the survival sub-model specification incorporates the association parameters to the selected Cox PH survival model.

As we can easily observe from the reported table 12 the estimated joint model parameter of the posterior estimates of the regression coefficients $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ together with their 95% credible intervals all of the estimated $\boldsymbol{\beta}$ values which was significant in the classical separate longitudinal part were here also have significant effects on the CD4 count measurements process of HIV/TB co-infected patients at 5% level of significance. But when we look at the estimated significances of $\boldsymbol{\gamma}$ parameters at 5% significance level WHO clinical stage IV ,weight and smoking have significant effect on the hazard function of time-to-death of co-infected patient when we look at the classical separate survival model covariate in relation with survival sub-model of the joint modeling the none significance of clinical stages in separate survival analysis have significant effect on hazard function of time to death since clinical stage IV have positive effect significance on the hazard function.

When we look at the estimated posterior mean of association parameters which associates longitudinally measured CD4 cells count measurements process to time-to-death of co-infected patients using shared random effect parameters the three association parameters that associates random intercept; random linear slope and random quadratic slope with to death of HIV/TB co-infected patients all of the three association parameters have significant effect on hazard of time-to-death since their 95% credible intervals excludes zero. The estimate of the association parameter due to the random intercept and random linear slope of CD4 count measurement $\hat{\alpha}_1$ = -0.0585 and $\hat{\alpha}_2$= -1.798 which was negative means that subject specific base line and linear slope of individual CD4 count measurement marker was negatively associated with the hazard of death; while the estimated values of the association parameter due to random quadratic slope $\hat{\alpha}_3$ = 0.2788 which was positive shows that the subject specific quadratic slope was positively associated with hazard function of survival time to death meaning that it increases the risk of death.

The estimated posterior values of survival sub-model together with the hazard ratio was reported table 13 below; as can be observed from the summary result of table 13 clinical stage IV and

smoking have positive impact on the survival hazard function and the computed hazard ration 15.5118 for clinical stage IV meaning the hazard rate of co-infected patient group of clinical stage IV group was 15.51 times than that of co-infected patient clinical stage I group at base line.

Table 13: Posterior estimated parameter values and hazard ratio estimates with their 95% credible intervals of the survival sub-model of the selected joint model

Base line Covariates	Survival estimates		HR estimates	
	Coeff ($\hat{\gamma}$)	95% CIs	HR	95% CIs
clinical stages				
Stage II	1.4028	[-1.1807,4.9895]	4.0665	[0.3071,146.8630]
Stage III	1.8983	[-0.6002,5.6984]	6.6745	[0.5487,298.3896]
Stage IV	2.7416	[0.4153,6.4328]*	15.5118	[1.5144,621.9129]*
Pulmonary TB	0.4056	[-0.5893,1.3048]	1.5002	[0.5547,3.6869]
weight	-0.0646	[-0.112,-0.0285]*	0.9374	[0.8943,0.9719]*
functional status				
Bed ridden	1.1505	[-0.2123,2.4392]	3.1598	[0.8087,11.4638]
Working	-1.3272	[-2.6341,0.0229]	0.2652	[0.0718,1.0232]
Smoker	1.3081	[0.3391,2.1127]*	3.6991	[1.4035,8.2705]*
marital status				
Married	-0.1798	[-1.5013,1.1710]	0.8354	[0.2228,3.2252]
Separated	1.0548	[-0.2374,2.4590]	2.8714	[0.7887,11.6931]
Single	-0.5006	[-1.9231,0.8197]	0.6062	[0.1461,2.2698]
Windowed	-2.3774	[-5.1558,-0.097]*	0.0928	[0.0057,0.9075]*
association parameters				
$\hat{\alpha}_o$	-0.0585	[-0.061,-0.0566]*	0.9432	[0.9417,0.9449]*
$\hat{\alpha}_1$	-1.7981	[-1.8249,-1.759]*	0.1656	[0.1612,0.1722]*
$\hat{\alpha}_2$	0.2788	[0.2114,0.3332]*	1.321543	[1.2354,1.3954]*

*Indicates significance of covariates at 5% level significance

The hazard ratio of smoker group 1.3081 shows the risk of death in smoker co-infected group was 30.81% higher than that of the none smoker co-infected patient group while the hazard ratio for the windowed marital status group 0.0928 shows that the hazard rate for the windowed

marital status group in comparison with divorced marital status group or the risk of death in windowed marital status group was 90.721% lower than that of divorced marital status group of co-infected patient.

The estimated associated parameter $\hat{\alpha}_0$ = -0.0585 shows the patient specific base line CD4 count measurement reduce the hazard rate by 0.9432 meaning that the co-infected patient with lower base line CD4 count measurement more likely to die than the co-infected patients with higher CD4 count measurement which shows the unit increment in base line reduces the risk of death by 0.9432 holding the effect of other covariates constant;$\hat{\alpha}_1$= -1.798 shows the patient specific slope reduce the hazard rate by 0.16563 meaning that with steeper increase in linear longitudinally measured CD4 count trajectories growth are less likely to die to die than the co-infected patient with steeper decrease in linear longitudinally measured CD4 count trajectories where as the $\hat{\alpha}_2$=0.2788 which associated the patient specific quadratic slope increases the hazard rate by 1.321543 for HIV/TB co-infected patient in the study area.

Finally; the diagnosis for the convergence of MCMC was also made using time series plots of figure 19 and 20 on annexes for the estimated parameters and the plots did not show any alarming convergence problems.

5. DISCUSSION

In this study, several statical modeling starting from classical linear modeling up to Bayesian approach of joint modeling of longitudinal CD4 measurements process and time-to-death of HIV/TB co-infected patients was presented. The joint modeling was base on Rizopoulos(2014) and Rizopoulos and others(2013) approaches. Recently joint models are utilized in follow-up studies where interest is in associating a longitudinal response with an event time outcome mainly when one is interested in measuring the strength of the association between the hazard of an event and a time-varying covariate, when we should pay special attention to the attributes of the covariate process. In particular, when this is an endogenous time-varying covariate Kalbeisch and Prentice (2002), standard methods, such as the time dependent Cox model Therneau and Grambsch (2000), are not optimal for measuring this association.

For instance, biomarkers or other parameters measured on patients during follow-up and the important feature of such covariates is that their existence and/or future path is directly related to the event status. By postulating a model for the joint distribution of the covariate and event processes we explicitly acknowledge this link, and hence we obtain a more accurate estimate for their association.

Consequently, the joint model proposed in this study relates the longitudinal CD4 measurements marker to time-to-death of HIV/TB co-infection in the study area and considers different shared parameter association structure for the survival sub-model simultaneously. Since joint model building usually starts from separate models for each component, initially each data are analyzed separately. The separate analysis used to specify the mean response of the model; random effects to be included in the longitudinal model and appropriate base line covariates for the separate survival model that was provided for the joint models.

In the separate analysis of the longitudinal data, first since the CD4 count measurements is a discrete (count data) it needs transformation to be continuous therefore; the square root transformation was used and its normality of was checked using box plots. After a square root transformation of the CD4 counts, the mean response of the longitudinal square root CD4 counts is determined using loess smoothing techniques suggests being linear and quadratic in time effects.

After transformation the data were analyzed using linear model to determine an appropriate fixed effect model for the linear mixed model and the resulted of linear model showed WHO clinical stages; use of alcohol; functional status; linear and quadratic time effects; weight and the interaction of linear and quadratic time effects with functional statuses have significant effects on CD4 count measurement of co-infected patients at 5% significant level.

After determination of the appropriate linear model with appropriate covariates using the AIC values of the models and log likelihood ratio tests for the fixed effects; the data was analyzed with linear mixed model which allows within and between subject sources of variation. To select an appropriate random effects; the selected fixed effects was fitted with different random effects starting from the random intercept to random intercept; linear and quadratic slopes and compared using AIC values of the fitted linear mixed model.

Among the seven fitted linear mixed models with different random effects the linear mixed model fitted with random intercept; linear and quadratic slopes which has a minimum AIC value in comparison with six remaining linear mixed models was considered as an appropriated linear mixed model. To improve this selected linear mixed model an appropriate covariates among the fixed effects of the fitted linear model was selected using AIC values since some of the covariates becomes none significant after accounting within subjects variation by the linear mixed model this is because of the classical linear model only considers the between subject variation.

The final selected linear mixed model also showed functional status; linear and quadratic time effects, weight and the interaction of working functional status with linear and quadratic time effects have significant effects on CD4 count measurements co-infected patients and the goodness of fit these model was also checked using the residual plot diagnosis tests the within and between variation assumption was satisfied and the selected linear mixed model for the longitudinal sub-model was good fit the data.

Turning to the separate survival analysis, the variables to be included in the survival model are determined using an automatic variable selection method using R for the semi parametric and parametric survival models. Then, of the all candidate covariates considered, WHO clinical stage; type of tuberculosis; base line weight; functional status; smoking status and marital status were extracted to be included in the survival models.

The parametric models; Weibull, Exponential, Loglogistic and Lognormal were compared using graphically and AIC values of the fitted models to select an appropriate parametric survival model. Then, the Weibull parametric which has minimum AIC values and looks good linear fit than the remaining parametric survival models was selected as an appropriate parametric survival model.

To have an appropriate among the selected parametric survival model (Weibull) and Cox PH both models were compared by the estimated base line probability curve plots as well as using the AIC values of the models was considered since the estimated probability by the Cox PH looks an appropriate estimates as well as the AIC values of Cox PH was very smaller than AIC values of Weibull parametric survival model therefore; we considered Cox PH as the final appropriate separate survival model of HIV/TB co-infected patients in the study area.

After the selecting the final separate survival model to be Cox PH is used in survival sub-model in the joint modeling. The separate survival models were fitted with both Cox and Weibull PH and both of the models showed that bed ridden functional status; smoking and separate marital status groups have positive effects on hazard function meaning that co-infected patients belongs to these groups have lower survival time than their base line category groups (ambulatory functional status, none smoker and divorced marital status groups respectively); Hailu (2012) and Tarekegn (2011) using Cox PH also found bed ridden functional status is the higher risk factor to HIV/TB co-infected patients where as working functional status group and base line weight have negative effects on survival hazard functions; Mohammed *et al* (2011) and Hailu (2012) found base line weight as the risk factor for the survival of HIV/TB co-infected patients this study also showed base line weight and working functional status in comparison with ambulatory functional status have direct relation with the survival time since they have negative effect on the hazard ratio of survival time of co-infected patients in the study area.

The proportional hazard assumption; the goodness of fit and the linearity structure were also checked using scheonfeld; cox snell and mertingle residual plots respectively for the adequacy of the fitted Cox PH survival model and they showed no problems of the fitted Cox PH model and the selected Cox PH model fit the survival time appropriately.

After the separate analyses using the separate longitudinal and survival model for the identification of an appropriate sub-model to be included in the joint modeling to have an

appropriate shared parameter association structure three association structures that relates longitudinal measured CD4 count markers with Cox PH model of time-to-death of HIV/TB co-infected patients were considered. Of these three candidate association structures first type of shared parameter structure associates the current underlying value of the longitudinally measured CD4 count marker at the same time point to the survival sub-model; the second type which associates the random effects and fixed effects corresponding to random effects of longitudinal sub-model to survival sub-model and the third associates only the random effect (subject specific) parameters of the longitudinal sub-model to the survival time for the joint modeling were considered.

Hence; the main aim was to associate the longitudinal measured CD4 count measurement marker of HIV/TB co-infected patients to their survival time we considered different random effects for the longitudinal sub-model for the three different shared parameter association structures that associated the longitudinal CD4 count process to the selected an appropriated Cox PH to have the appropriate shared parameter that relates the two processes to have an appropriate joint model based on DIC score.

Of the several fitted joint models; we considered the joint model which was fitted with random slope; linear and quadratic slopes for the longitudinal sharing only the random effects for the survival sub model as an appropriate joint model since this model have minimum DIC score than the remaining joint models. This final selected joint model relates the time-to-death with the base line subject specific CD4 count measurement and subject specific linear and quadratic slopes of CD4 count measurements marker of HIV/TB co-infected patient in the study area.

As described earlier; the model is factorized as two sub-models; marginal longitudinal model for longitudinal CD4 count measurements and a conditional (given the longitudinal data) survival model for the risk of death from HIV/TB co-infection for joint models are estimated under Bayesian framework using a single chain of 75,000 MCMC iterations from which we discarded the first 35,000 samples as burn-in; finally trace time series plots were used for the convergence diagnosis of MCMC samples and the plots did not show any alarming indications of convergence failure.

The impact of CD4 cell count on survival rate has been assessed by several studies indicating that the depletion of CD4 cell count is associated with high risk of death D Zenner, S Conti, Z

Yin, *et al.* (2013), Catala *et al*. (2011) and Hailu (2012) found lower CD4 count measurement is the risk factor the survival of HIV/TB co-infected patients this study also found lower base line CD4 count measurement; steeper decrease in linear growth of CD4 and steeper increase in quadratic growth of CD4 count measurement of HIV/TB co-infected patients is the high risk factor for the survival of HIV/TB co-infected patients. Mohammed *et al.* (2011);Tarekegn(2011) and Hailu(2012) found WHO clinical stage categories were the risk factors for survival HIV/TB co-infected patients the joint model of this study also showed WHO clinical stage IV significant effect on hazard function and the hazard rate is higher in this clinical stage category when compared to WHO clinical stage I co-infected patient groups at base line.

6. CONCLUSION AND RECOMMENDATION

6.1. Conclusion

In this study, the classical methods of the estimated linear model showed at base line clinical stage III and stage IV; use alcohol and bed ridden functional status groups of co-infected patient groups have lower CD4 count measurement when compared to clinical stage I and stage II; who do not use alcohol and ambulatory co-infected patient groups respectively; where as the working functional status co-infected patient group have greater CD4 count measurement compared to the ambulatory functional status groups but the longitudinally measured weight have positive effect on CD4 count measurement. Additionally the linear model showed linear time have positive effect where as it negative effect when interacting with weight and functional status and the quadratic time effect have negative effect where as it have positive effect when interacting with weight and factional status of co-infected patients.

The separate estimated linear mixed model which accounts the within and between subject variation improves the classical linear model and functional status and its interaction with time effect which have significant effect without considering between subject variation in the linear model are excluded from the linear mixed model since they do not have significant effect at 5% level of significant. Linear and quadratic time effect; weight and functional status groups with time effect interaction were identified covariates by the linear mixed model that affect the CD4 measurement of HIV/TB co-infected patients at 5% level of significance.

The Cox and Weibull PH separate survival model indentified weight and working functional status group were the indentified covariates for the survival model that have negative effect on hazard function of survival time; where as bed ridden functional status group; use of smoking and separate marital status groups in comparison with ambulatory functional status group; none smoker and divorced marital status groups respectively have positive effects on hazard function of survival time that lowers the survival time of HIV/TB co-infected patients at 5% level of significance in the study area.

The estimated joint model with the Bayesian approach showed that the shared random effect parameters are appropriate for the joint modeling for longitudinally measured CD4 count and with time-to-death processes of HIV/TB co-infected patients in the study area. The estimated

model further showed that the patient specific base line CD4 count and patients' specific (random) linear slope of CD count were negatively associated with hazard function where as the patient specific quadratic slope CD4 count was positively associated with hazard function of HIV/TB co-infected patients have significant effects at 5% level of significance.

6.2. Recommendations

The base line of CD4 count measurement has positively associated with survival time. However; being bed ridden lowers the base line CD4 count measurement so that the co-infected patient should be care full when they are in the bed ridden functional status during co-infection period.

Since the risk of death is higher in smoker groups; being in IV WHO clinical stage and separated marital status groups the concerned bodies or the co-infected patient should be cautious when in this category during HIV/TB co-infection period.

The slope of quadratic time effect of the CD4 count measurement is also another risk factor which has positive effect on hazard function meaning that it lower the survival time of HIV/TB co-infected patient therefore the co-infected patients take care of when the quadratic growth slope of CD4 count measurement is higher.

Since the longitudinally measured CD4 count measurement process is related to time-to-death process of HIV/TB co-infected patients joint modeling is an appropriate setting to relate the patient specific longitudinal measured CD4 count marker process to the time-to-death which the separate modeling could not handle.

HIV/TB co-infection is the most serious problem that lowers the survival time of co-infected patients. Therefore, the governmental and nongovernmental organization should also give attentions by giving consultancy services on the above identified risks factors on the survival time of co-infected patients. Moreover, academician who wants to study further on HIV/TB co-infections is better to see TB as recurrent event, mainly because of even TB can be cured in HIV infected patients and again it re infected the patients when the CD4 counts becomes lower than expected this is due to CD4 count process might be not the same during co-infection period and when TB is cured in HIV infected patients.

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8. ANNEXES

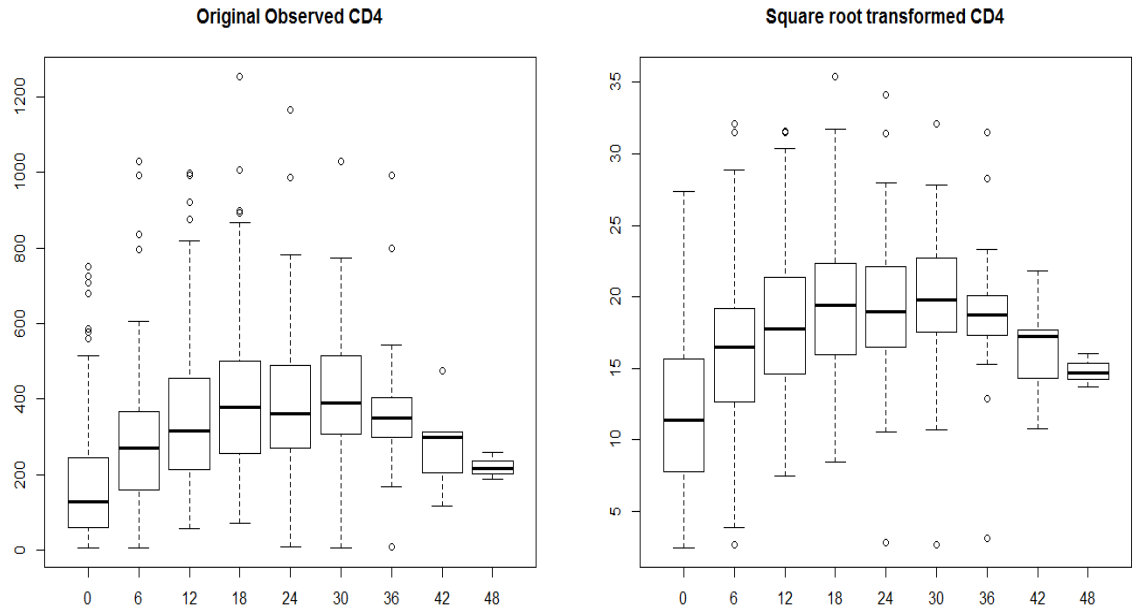


Figure 5: CD4 count measurement versus time quartile-quartile plot for the original and square root transformed data for the normality check

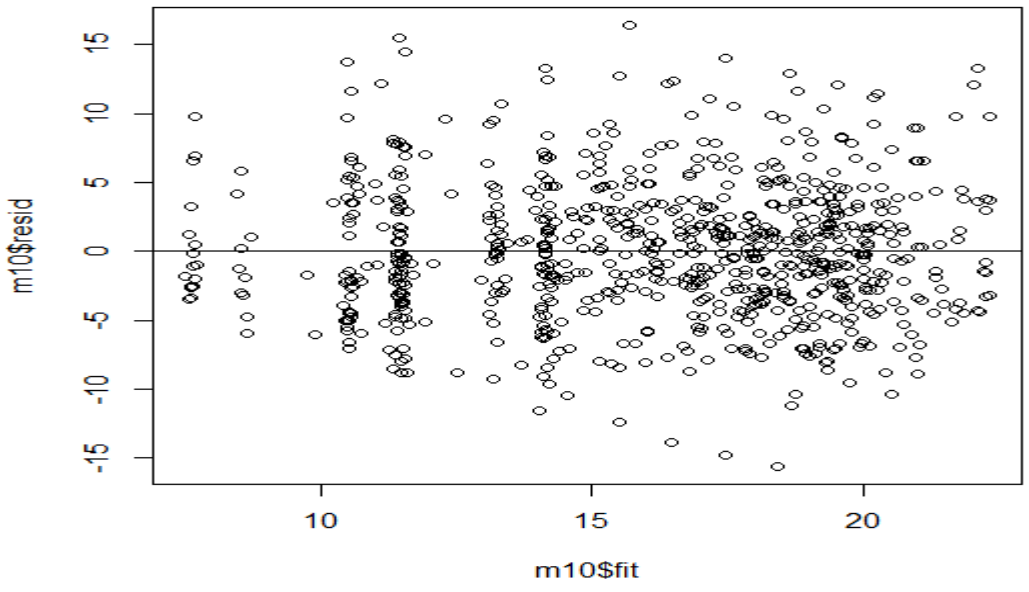


Figure 6: Residual versus fitted values of the estimated linear model for constant variance of residuals

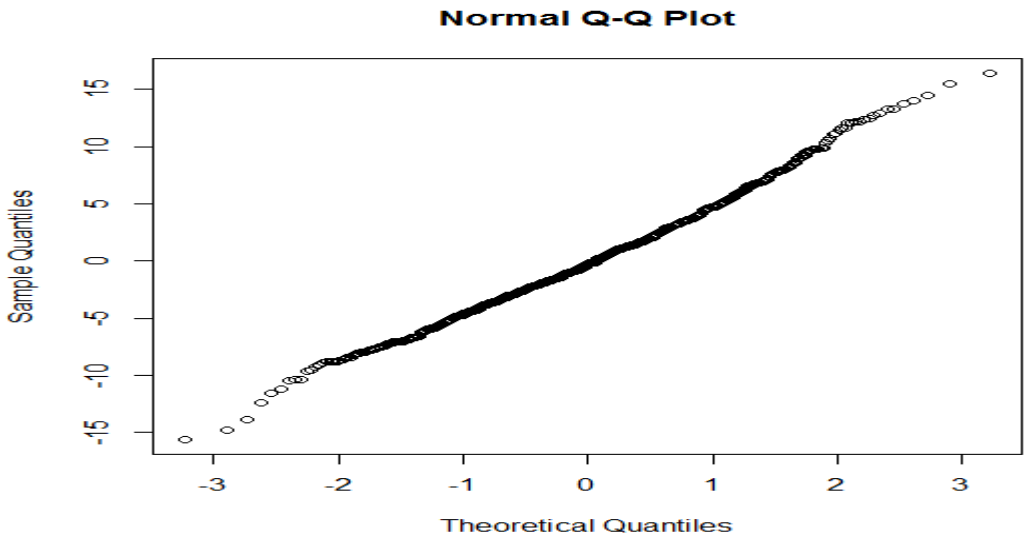


Figure 7: Quartile-quartile plot of the residual for the normality check of error term for the fitted linear model

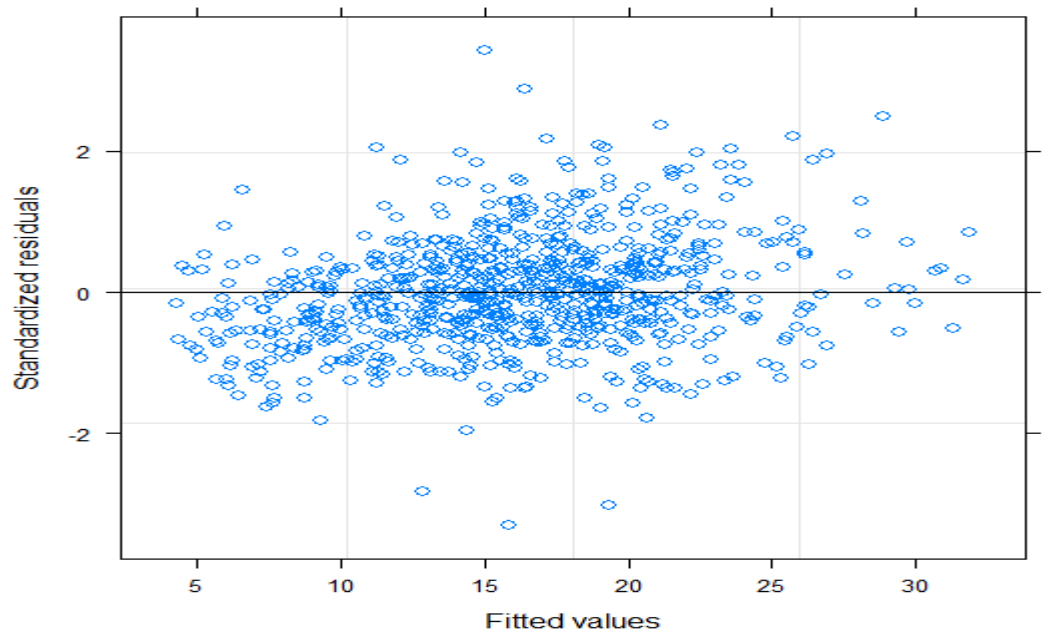


Figure 8: Residual versus fitted values of within group error term of linear mixed model

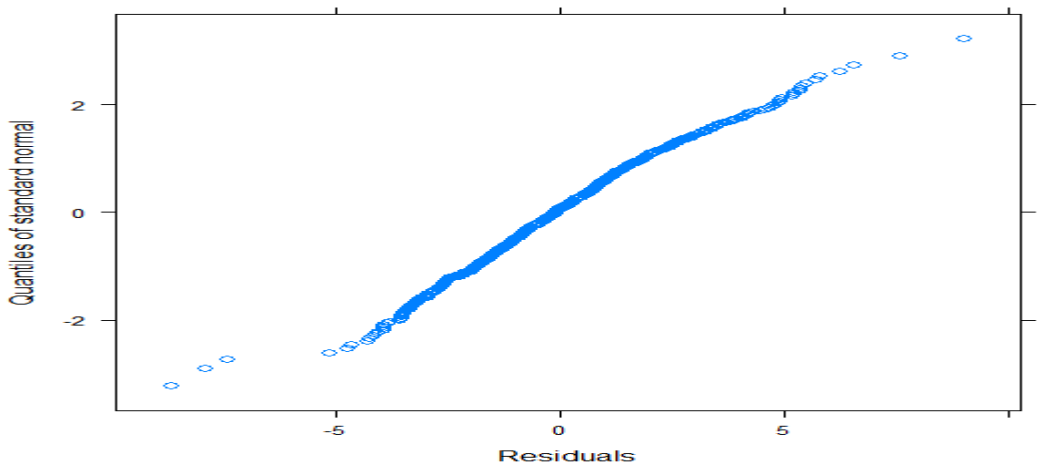


Figure 9: Quantile-quantile plots for the normality within group error of the fitted linear mixed model

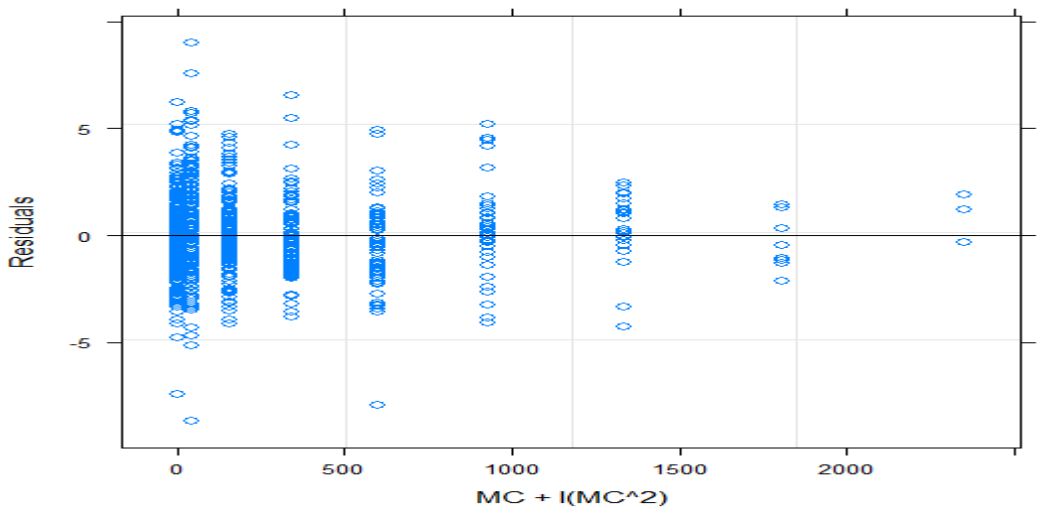


Figure 10: Residual versus fitted values for the random effects of the fitted linear mixed model

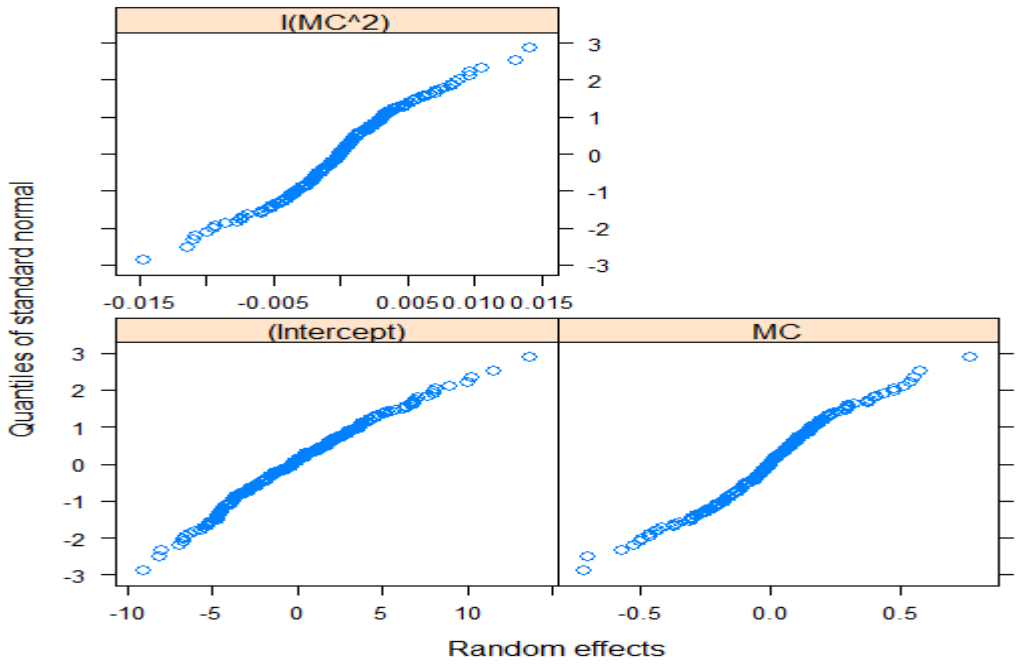


Figure 11: Standardized quantile-quantile plots for the normality of random effects of the linear mixed model where MC denotes used to represent time during analysis in the R-code

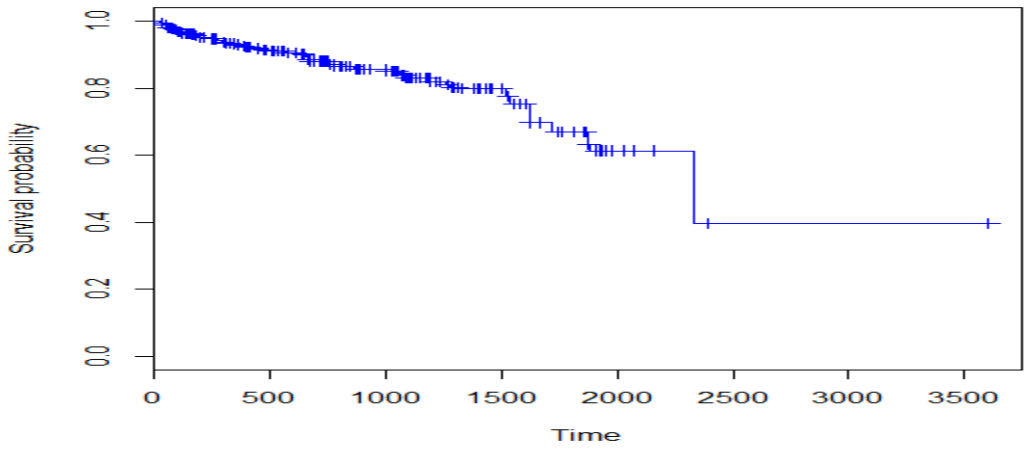


Figure 12: Estimated Kaplan-Meir survival probability plot versus time plots

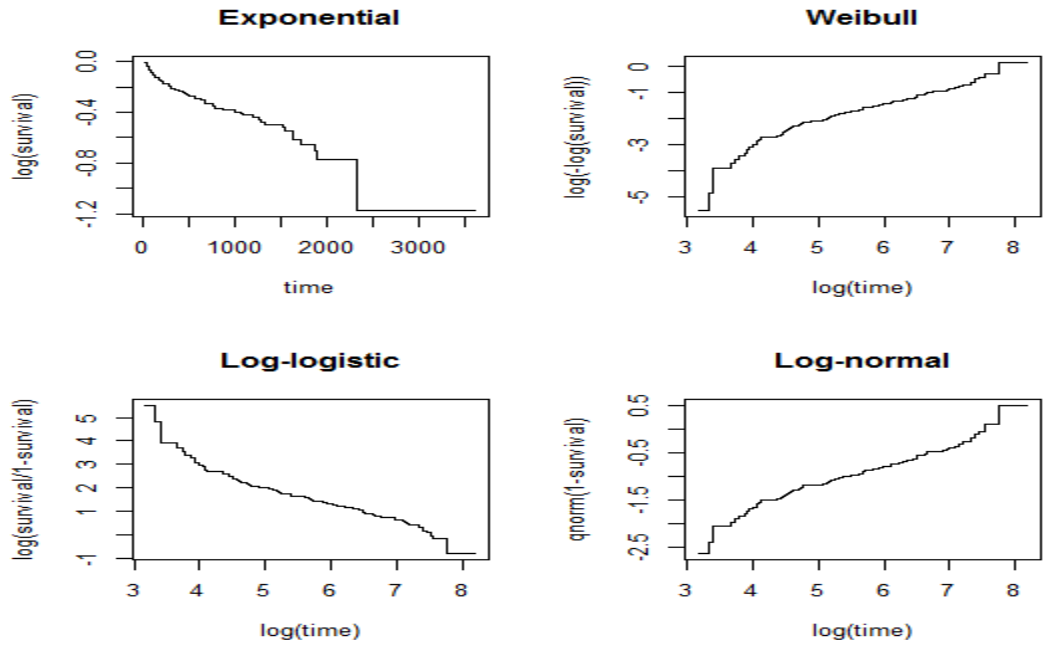


Figure 13: Function of Kaplan Meir probability estimate versus function time plots used for the identification of appropriate linearity structure to fit the survival time models

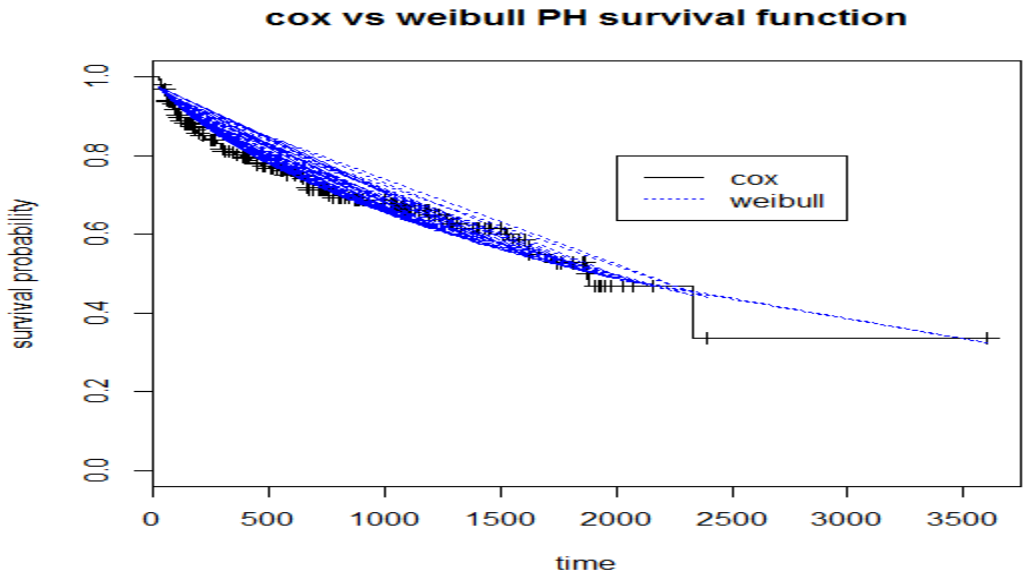


Figure 14: Cox versus Weibull estimated survival probability curve with the base line hazard

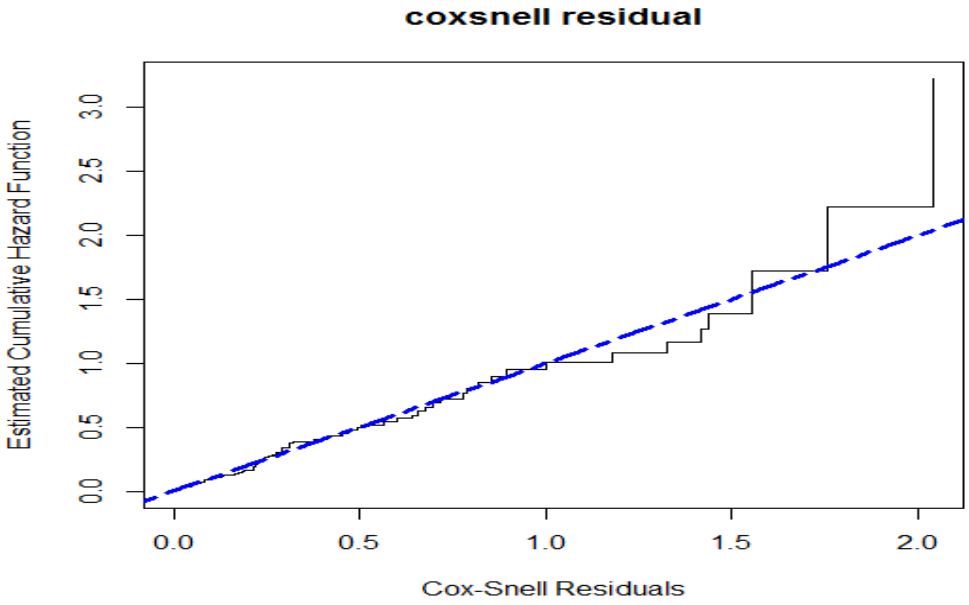


Figure 15: Cox snell residual plot for goodness of the fitted Cox PH survival model

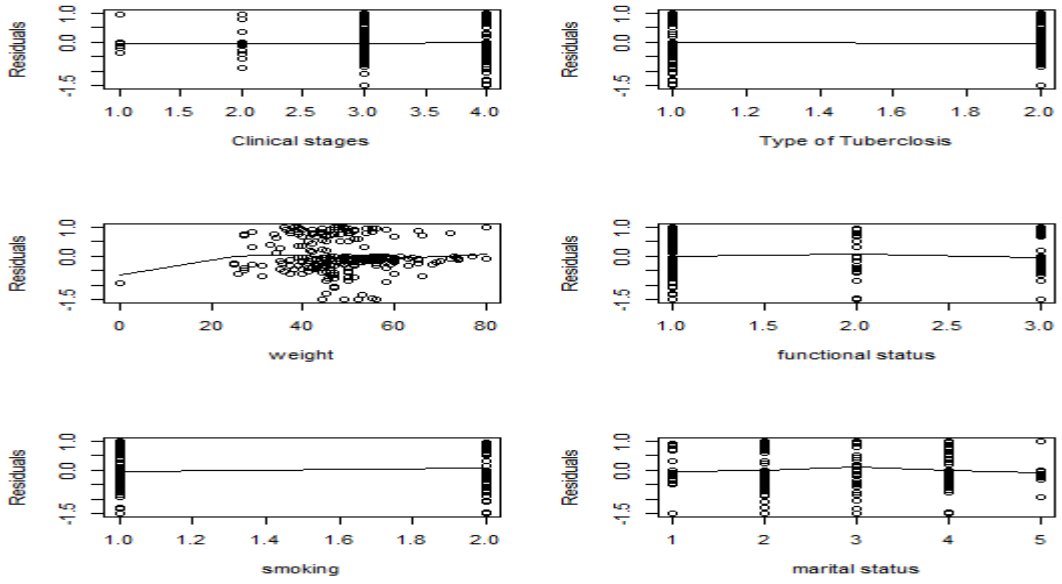


Figure 16: Martingale residual plots of the covariates used in Cox PH model to test the linearity structures

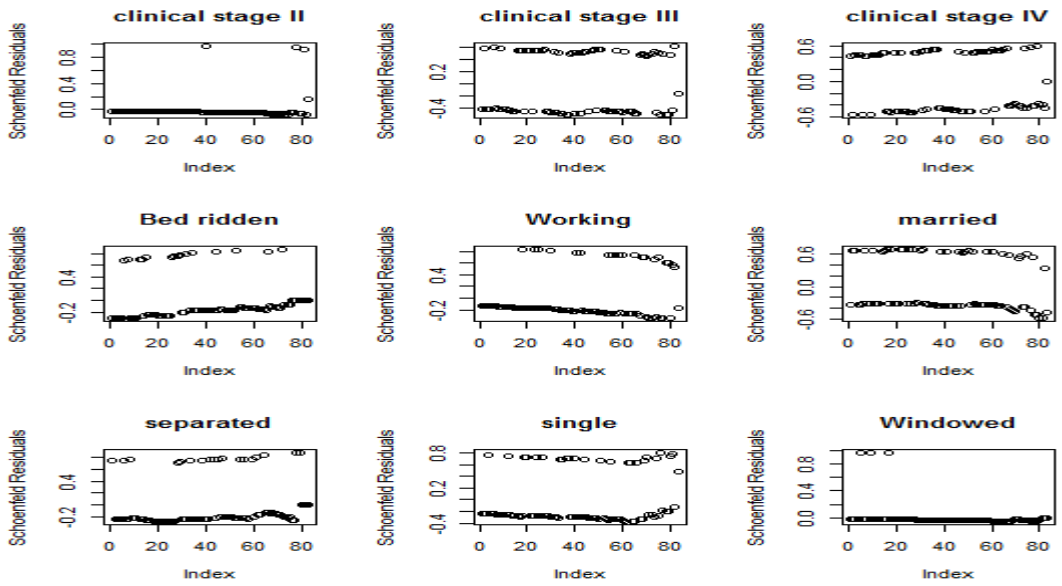


Figure 17: Schoenfield residual plots of the covariates plot for Cox PH assumption tests

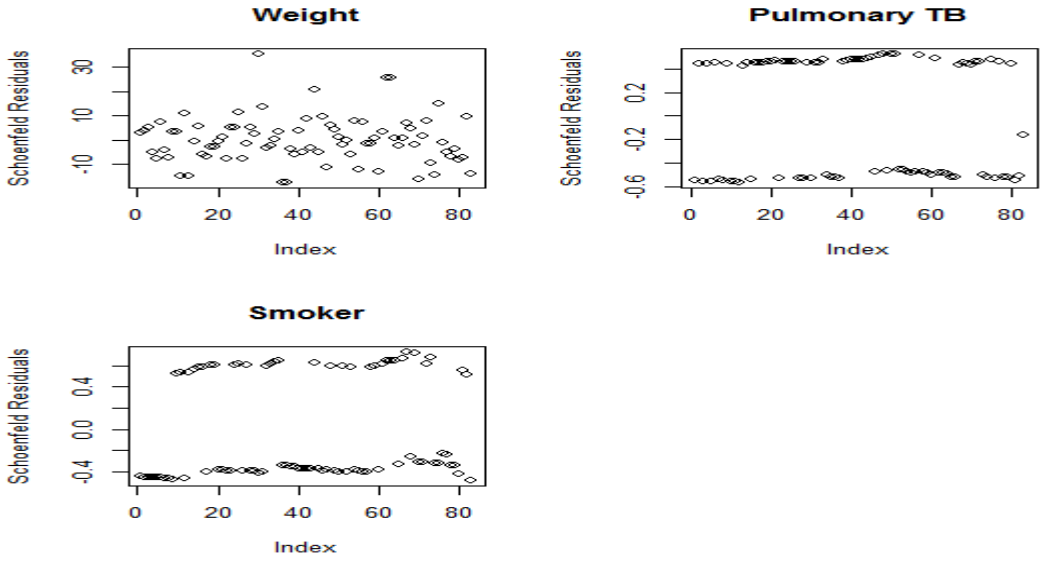
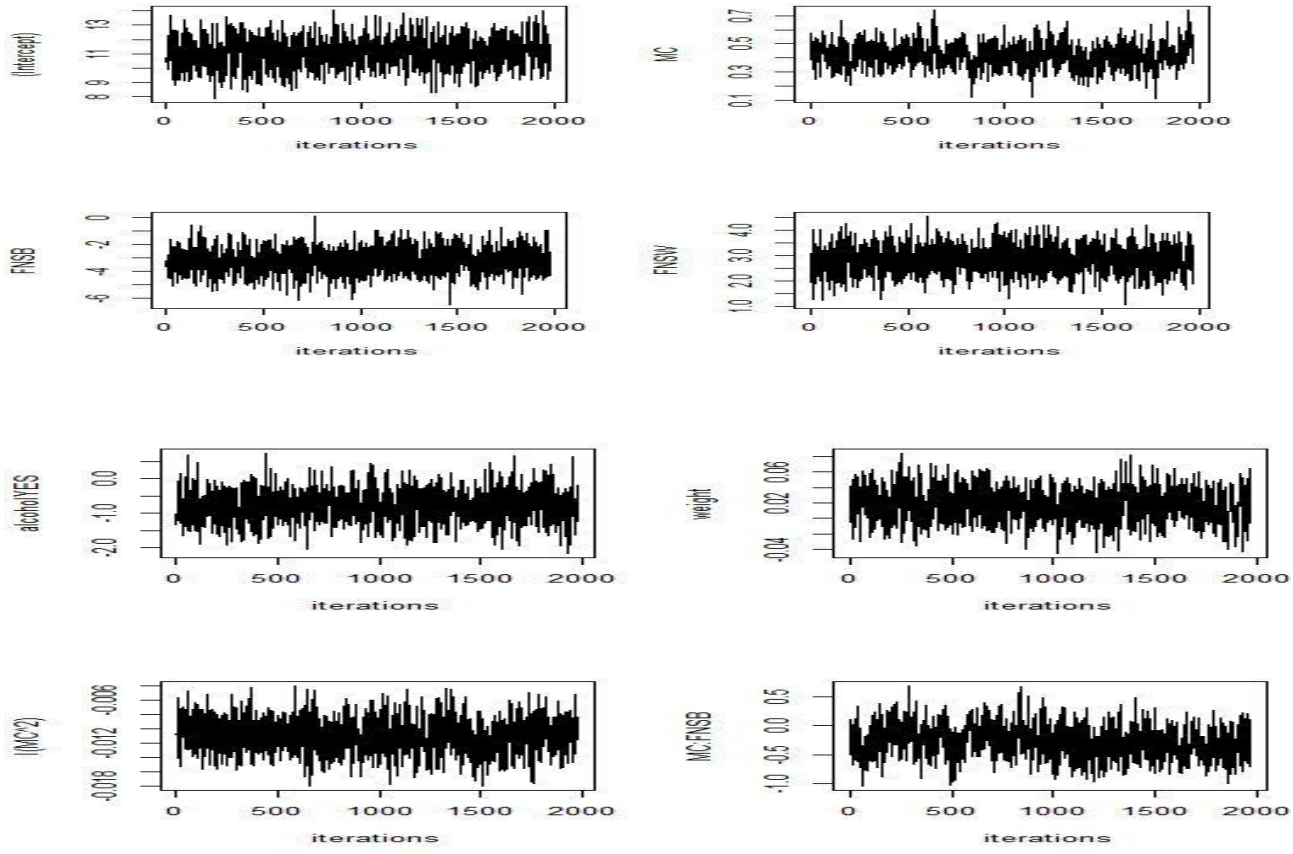


Figure 18: Schoenfield residual plots for the Cox PH assumption test


(Intercept)
MC
FNSB
FNSW
alcoholYES
weight
I(MC^2)
MC:FNSB
MC:FNSW
FNSB:I(MC^2)
FNSW:I(MC^2)
sigma
iterations

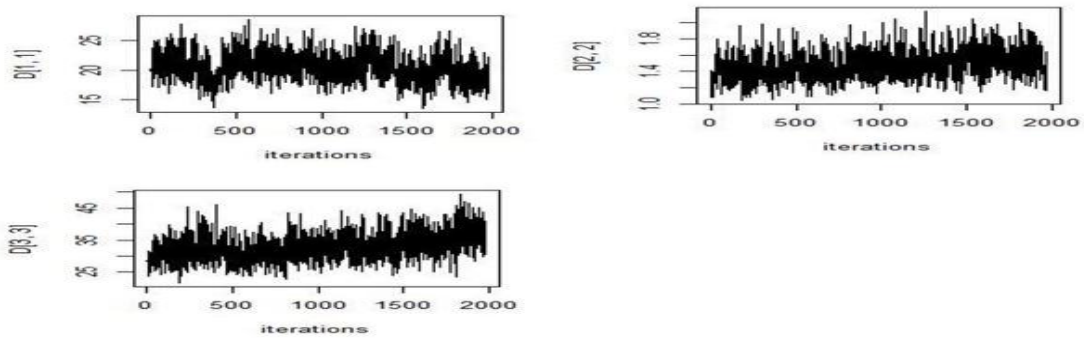
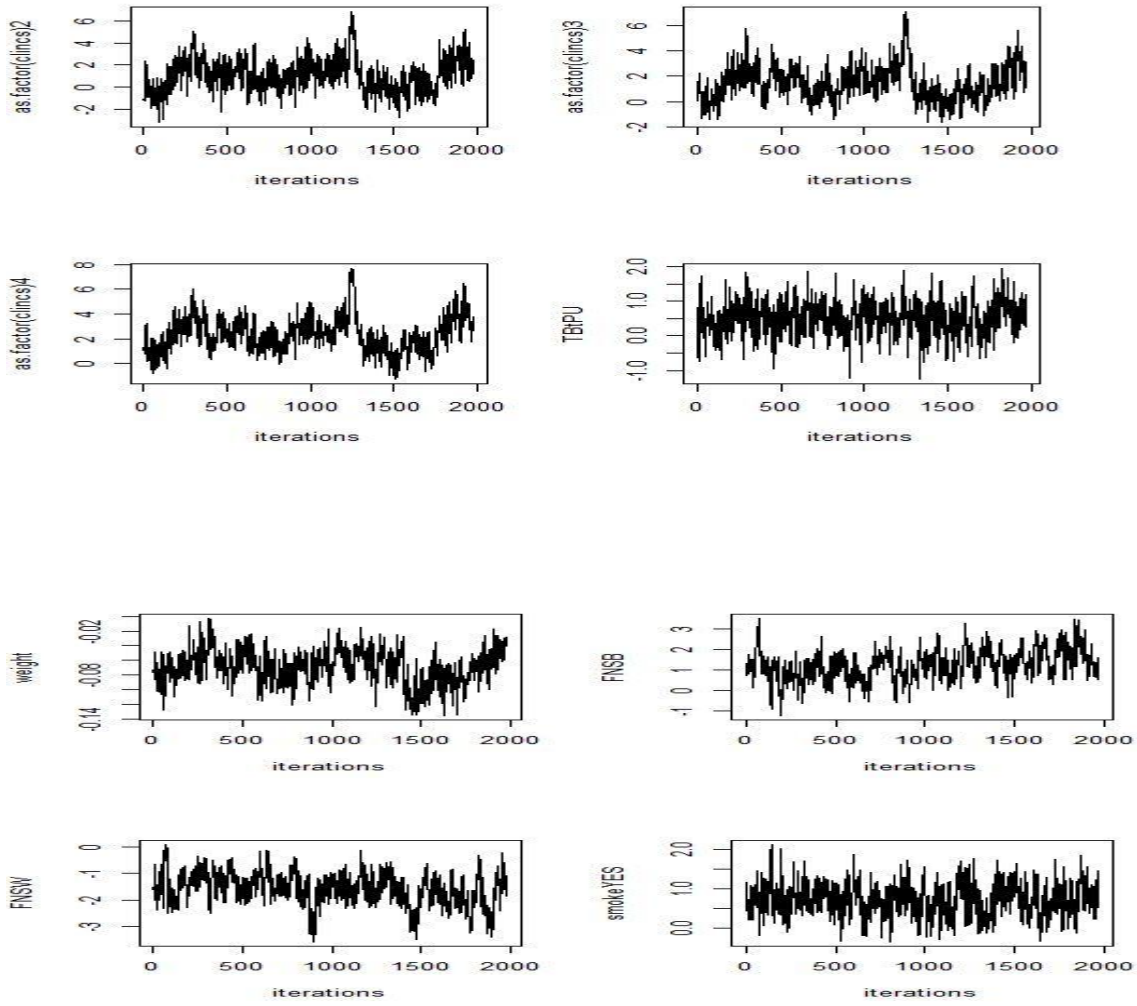


Figure 19: Longitudinal sub-model MCMC samples convergence diagnosis plots



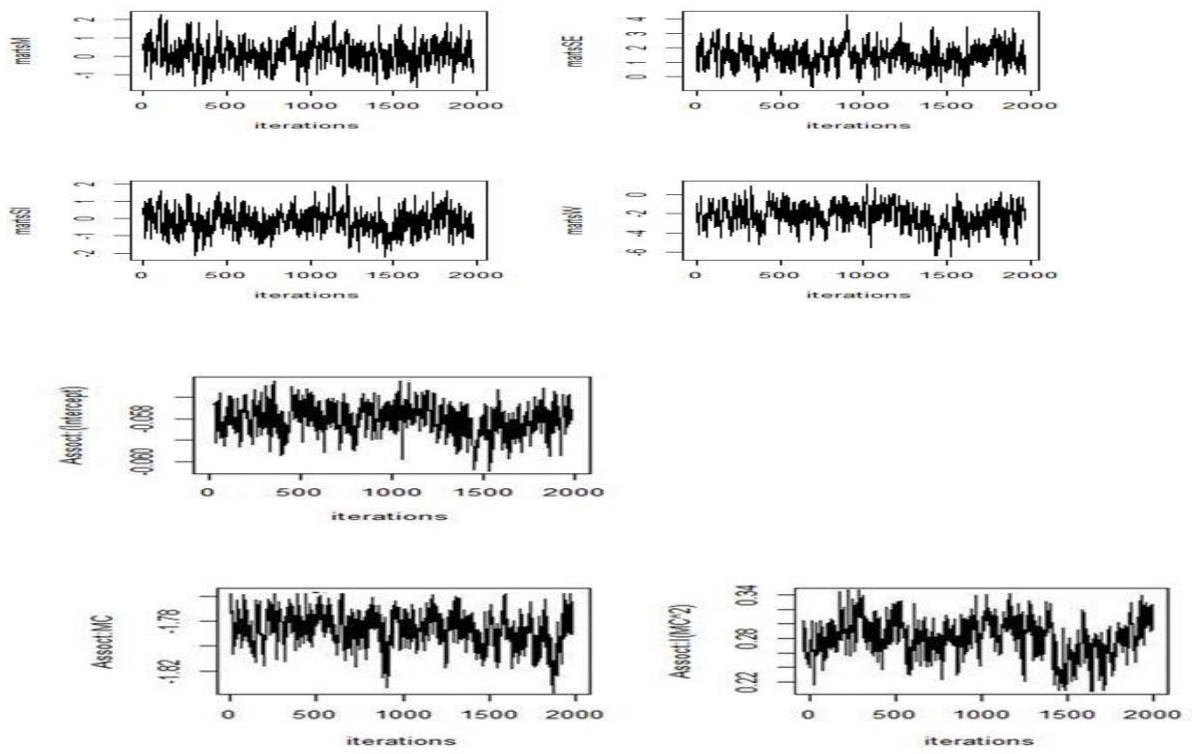


Figure 20: Survival sub-model MCMC samples convergence diagnosis plots

Table 14: Test for Cox PH assumption numerically

covariates	rho	chisq	p
clinical stage			
stage II	0.1343	1.5455	0.2138
stage III	0.1289	1.4719	0.22505
Stage IV	0.0234	0.0459	0.83033
Functional status			
Bed ridden	0.0644	0.4047	0.5247
Working	0.2464	1.9947	0.2543
marital status			
married	-0.1026	0.924	0.33642
separated	0.0315	0.0877	0.76717
single	0.0377	0.1245	0.72418
windowed	-0.2029	0.8961	0.484
weight	-0.1283	1.5888	0.2075
pulmonary TB	-0.2895	1.8007	0.311
Smoker	0.0769	0.6537	0.41879
GLOBAL	NA	25.5084	0.01259

Table 15: The mean and variance for square root of CD4 cells count measurement at each time points for some selected categorical covariates

Time points in months		0	6	12	18	24	30	36	42	48
Mean	A	11.10	15.73	17.81	19.56	19.88	19.08	18.05	15.26	15.38
	B	7.95	10.71	13.82	13.42	10.54	13.64	15.30	NA	NA
	W	13.93	17.22	18.58	19.75	19.07	20.99	19.74	17.21	13.71
Variance	A	27.85	23.32	21.65	21.32	20.79	19.56	7.23	7.98	0.93
	B	15.15	32.51	30.04	16.80	NA	NA	NA	NA	NA
	W	25.02	27.11	24.19	27.18	32.54	41.15	44.19	15.49	NA
WHO clinical stages										
Mean	1	12.91	16.02	19.06	19.01	12.07	16.22	15.71	10.77	13.71
	2	15.25	17.43	18.29	19.97	19.64	19.51	19.54	17.46	15.38
	3	11.52	15.52	18.01	18.80	19.35	19.21	17.95	15.82	13.71
	4	11.55	16.38	17.98	20.03	19.99	22.28	20.97	21.82	15.38
Variance	1	29.51	30.99	28.78	61.59	170.73	151.54	315.11	NA	NA
	2	27.28	17.38	16.20	13.58	11.81	24.36	0.22	NA	0.93
	3	21.24	32.87	27.31	22.05	24.61	17.25	6.18	3.72	NA
	4	36.40	25.93	22.38	30.17	26.91	33.71	29.67	0.00	0.93
Use of alcohol										
Mean	NO	12.21	16.81	18.66	19.54	20.18	19.94	18.62	17.13	14.20
	YES	11.44	14.72	17.01	19.16	17.45	19.63	19.30	16.06	16.06
Variance	NO	28.82	24.75	23.40	26.34	29.80	34.29	38.94	19.94	0.49
	YES	28.82	32.52	22.49	22.95	14.16	23.76	13.50	2.39	NA
Smoking status										
Mean	NO	12.14	16.53	18.43	19.67	19.78	19.70	18.55	16.72	14.20
	YES	11.23	14.72	16.55	18.43	16.91	20.48	19.82	17.26	16.06
Variance	NO	28.87	24.25	23.68	25.57	28.19	32.76	32.04	15.22	0.49
	YES	28.60	39.30	20.83	22.83	10.26	21.74	19.40	NA	NA

*Note that

Functional status	WHO Clinical stages
A= ambulatory	1= stage I
B= bed ridden	2= stage II
W=working	3= stage III
	4=stage IV

Table 16: Univariate Cox PH analysis results

Base line covariates	Survival estimates			Hazard ratio estimates	
	Estimated	Standard error	95% CIs	Estimated	95% CIs
sex male	0.09584	0.22293	(-0.3411,0.532769)	1.101	(0.711,1.704)
age	0.005716	0.012229	(-0.01825,0.029685)	1.006	(0.9819,1.03)
CD4	-0.00256	0.000904	(-0.00433,-0.00079)*	0.9974	(0.9957,0.9992)*
weight	-0.02853	0.009763	(-0.04766,-0.0094)*	0.9719	(0.9535,0.9906)*
alcohol user	0.6749	0.2204	(0.242935,1.10693)*	1.964	(1.275,3.025)*
smoker	0.7226	0.2264	(0.278838,1.16629)*	2.06	(1.322,3.21)*
drug	0.7268	0.237	(0.262288,1.19130)*	2.068	(1.3,3.291)*
pulmonary TB	0.03201	0.22	(-0.39919,0.463209)	1.033	(0.6709,1.589)
urban resident	0.09793	0.32443	(-0.53794,0.733796)	1.103	(0.5839,2.083)
Educational level					
primary	-0.4488	0.2809	(-0.99935,0.101725)	0.6384	(0.3681,1.107)
secondary	-0.273	0.2941	(-0.84946,0.303524)	0.7611	(0.4276,1.355)
tertiary	-0.1024	0.4977	(-1.07797,0.873098)	0.9026	(0.3403,2.394)
Marital status					
married	-0.4566	0.3983	(-1.23727,0.324119)	0.6334	(0.2902,1.383)
separated	0.5781	0.4266	(-0.25794,1.414128)	1.7826	(0.7726,4.113)
single	-0.3156	0.4097	(-1.11863,0.487372)	0.7293	(0.3267,1.628)
windowed	-0.955	0.6779	(-2.28363,0.373688)	0.3848	(0.1019,1.453)
Working time					
part time	-0.00448	0.7319	(-1.43897,1.430021)	0.9955	(0.2372,4.179)
unemployed	0.213069	0.470336	(-0.70877,1.134911)	1.2375	(0.4922,3.111)
full time	0.04322	0.507084	(-0.95065,1.037087)	1.0442	(0.3865,2.821)
Functional status					
Bed ridden	1.0091	0.3015	(0.418187,1.59995)*	2.743	(1.5192,4.9528)*
Working	-0.9643	0.2709	(-1.49521,-0.43349)*	0.3812	(0.2242,0.6482)*
WHO clinical stage					
Stage II	0.4967	1.1267	(-1.71163,2.704958)	1.643	(0.1806,14.95)
Stage III	1.4581	1.0174	(-0.53586,3.452111)	4.298	(0.5852,31.57)
Stage IV	1.7976	1.0173	(-0.19625,3.791376)	6.035	(0.8218,44.32)

*Indicates significance of the covariates at 5% level significance