Outcome of chronic HIV-1 patients who interrupt their highly active antiretroviral treatments

Mubasiru-Asafe Lamidi

promotor :
Prof. dr. Ziv SHKEDY, Dr. Eric FLORENCE,
Mr. Joris MENTEN

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Outcome of Chronic Hiv-1 Patients who interrupt their Highly Active Antiretroviral Treatments

by

LAMIDI, MUBASIRU ASAFE

Dr. FLORENCE Eric

External Supervisor 1

Mr. MENTEN Joris

External Supervisor 2

Prof. (dr.) SHKEDY Ziv

Internal Supervisor

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Certification

This is to certify that this project was carried out by LAMIDI Mubasiru Asafe under our thorough supervisions and reflects his true research ability.

LAMIDI Mubasiru Asafe

Student

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Signature

Dr. FLORENCE Eric

External Supervisor 1

……..

Signature

Mr. MENTEN Joris

External Supervisor 2

…….

Signature

Prof. (dr.) SHKEDY Ziv

Internal Supervisor

……..

Signature

Dedication

To my late mother……..

who taught me the virtues of knowledge and the vices of ignorance

and

To my late father……..

who taught me how to respect the opinions of others

(May their gentle soul rest in perfect peace)

Abstract

***Introduction*:** Highly active antiretroviral treatments (HAART) have become a *sin qua non* in the live of HIV/AIDS patients most especially for those that have access to it in the developed world. It has become an unfulfilled dream for those in developing world due to their cost that may not be afforded by the concern patients. Some chronic HIV-1 patients at Institute of Tropical Medicine, Antwerp, Belgium are having their treatments interrupted for reasons other than treatment failure.

Objective of the study: The objectives of the study were to examine the outcome of the patients with chronic HIV-1 infection who interrupt their highly active antiretroviral treatments for reasons other than treatment failure, in terms of rebound of plasma viral loads and decrease in CD4 cell counts and come up with risk factors that are predictive of 'good control' of the infection.

Methodology: Apart from using exploratoy data analysis with inclusion of nonparametric Kapla-Meier survivorship estimates to compare the risk groups, two major ways of dealing with survival data are used in achieving the desired objectives which are Cox proportional hazards regression model for right censored-data and Weibull parametric regression model for interval censored-data based on the fact that the viral load and CD4 counts are not constantly monitored but are only measured every 3 to 6 months, the exact time of treatment failure is unknown.

Results: Of the 1296 patients in the follow-up study, 148 had such treatments interruption since 2000. We found that the median failure time for the patients is 2 and 3 months respective for viral and immunological failures. The following variables are identified as risk factors predicting viral and immunological failures; viral load at start HAART on log scale, duration of the disease on log scale, duration of treatment interruption, CD4 at start HAART, percentage change in CD4 cell counts and continent of origin. For some of these variables, they reduce the hazard of having viral and CD4 failure with about 8% while some increase the hazards of failure by more than 100%.

Conclusion: The findings from this study show that treatments interruption of at least three months worsen disease outcome. The results suggest that interruptions might be risky, particularly when there is viral rebound of more than 1000 copies/µl and CD4 cell counts less than 20%.

Keywords: viral failure, interval-censored, right-censored, Cox proportional model, Weibull regression model

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1.0 Introduction

1.1 Historical Background

Early in 1981 among epidemics, two-dozens of new heterogeneous diseases began to strike non-randomly growing numbers of male homosexuals and male intravenous drug users in the United State and Europe. Assuming immunodeficiency as the common denominator, the US department of disease control termed the disease as Acquired ImmunoDeficiency Syndrome (AIDS). From 1981-1984 many researchers proposed that this disease was as a result of recreational drug use because of the exact correlations and of drug specific diseases. Among the diseases that were found to have high correlation with AIDS are Kaposi's sarcoma, Bacteria and Fungi pneumonia, Oral yeast infections, dementia, diarrhea, tuberculosis, herpes, lymphoma, weight loss, toxoplasmosis, chronic fever etc. (Duesberg, Koehnlein and Rasnick 2003). However, in 1984 the it was proposed that a virus now termed Human Immunodeficiency Virus (HIV), is the causative agent of the epidemics of the US and Europe but also of a new epidemic in Africa.

According to global summary of AIDS epidemic in December 2006 by WHO report, there were a total of 39.5million people living with HIV [95% CI (34.1 – 47.1million)] out of which there were 37.2 million adults [95% CI (32.1 – 44.5million)], 17.7 million women [95% CI (15.1 – 20.9 million)] and 2.3 million children under 15years of age with [95% CI (1.7 – 3.5 million)]. In the year 2006, a total of 4.3 million people were infected with HIV/AIDS among which are 3.8 million adults [95% CI (3.6 – 6.6 million)], and 530,000 children under 15 years of age with 95% confidence interval of (410,000 – 660, 000). In the same years in context, there were 2.9 million people who died of AIDS [95% CI (2.5 – 3.5 million)] out of which were 2.6 million adults [95% CI (2.2 – 3.0 million)] and 380,000 children below 15years of age [95% CI (290,000 – 500,000)].

In the last two years, as reported by WHO global AIDS statistics, there was remarkable increase in the number of people living with HIV/AIDS worldwide with significant increment reported at East Asia and Eastern Europe (WHO, 2006) where the number of people living with HIV/AIDS in 2006 was about 21% higher than those found in 2004. Despite all the efforts by international organizations to reduce the incidence of HIV/AIDS, there is a continuous growth in the number of people living with HIV/AIDS likewise the number of death recorded as a result of AIDS epidemic. For instance, in 2004 there were 36.9 million people living with HIV/AIDS which is lesser than that recorded in December 2006. The figure shows an increase of about 2.6 million. In addition, the death from HIV/AIDS recorded in 2004 was 2.7million compare to 2.9 recorded in December 2006.

1.2 Infection and Transmission of HIV/AIDS

Infection is aided by Langerhans cells in mucosal epithelial surfaces which can become infected. The CD4+ T-lymphocytes have surface receptors to which HIV can attach to promote entry into the cell. The infection extends to lymphoid tissues known as mucosa-associated lymphoid tissue (MALT), which contain follicular dendritic cells that can become infected and provide a reservoir for continuing infection of CD4+ T-lymphocytes. HIV transmission most likely requires HIV-infected cells, such as macrophages, lymphocyte, which enters the body through micro abrasions of the mucous membranes or through penetration of the skin with a needle. Infection is also aided by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation.

T-lymphocytes (or T-cells) are white blood cells in the body that play prominent roles in the immune system. There are two types of T-lymphocytes known as a type with molecule called CD4 on its surface while the other is one with molecule called CD8 which destroys cells that are infected and produced antiviral substance. When HIV infects humans, the cell it infects most often is CD4 cells. The virus becomes part of the cells and when the cell multiplies to fight an infection, this virus also multiplies. When someone is infected with HIV for a long time, the CD4 count goes down. This is a symptom that the immune system is weakened. The lower the CD4 count, the more likely the person will get sick. These CD4 cells bounces a lot due to so many factors such as time of the day, fatigue, and stress which can affect the test result. It is highly recommended by group of experts that it is better to have the blood sampled at the same time of the day and using the same laboratory.

The CD4 cell test is normally reported as the number of cells in a cubic millimeter of blood, or mm^3. Though there is some disagreement among medical experts about the normal range for CD4 cell counts, however, normal counts are between 500 and 1600. CD4 counts drop down drastically in people with HIV, in some cases down to zero. Because of variations normally observed in CD4 cell counts, some health care providers prefer reporting of the counts in terms of percentages based on the fact that it is assumed to be more stable than the number of CD4 cells. The normal range is between 20% and 40%. A CD4 percentage below 14% indicates serious immune damage. This is a sign of AIDS in people with HIV infection according to the US centers for Disease Control.

CD4 counts are used jointly with viral load to estimate how long someone will stay healthy. CD4 counts are also used to determine when to start certain types of drug therapy. When CD4 counts

goes down below 350, most health care providers start antiretroviral therapy (ART) or CD4 percentage going down below 15% as a sign to start aggressive ART, even when CD4 count is high. Some conservative health care providers wait till CD4 cell counts go below 200 and recent studies shows that starting ART treatment with CD4 percentage of below 5% strongly resulted in poor outcome.

Because they are such an important indicator of the strength of the immune system in the body, official treatment guideline in the US suggest that CD4 counts be monitored every 3 to 4 months.

1.2.1 Mode of Transmission

The major modes of transmission known worldwide are basically of the following. HIV/AIDS can be transmitted through indiscriminate sex without the use of condom either vaginal or anal sex. Also there can be a transmission of the infection through having contact with the blood of someone who has HIV. This can be through blood transfusion or use of razor blade that had already been used by HIV patient. HIV can easily be transmitted from a mother who has the disease to her baby during the pregnancy or child birth or during the breast feeding period. Also a patient who receives an unsterilized needle that was previously used by HIV patient is highly susceptible to the disease. Record shows that heterosexual transmission is the route by which most people with AIDS have become infected with HIV worldwide.

1.2.2 Highly Active Antiretroviral Treatment (HAART)

Since the discovery of HIV/AIDS 26 years ago, more than 25 million people have died of the infection (NIH, 2006) and more than 40 million are currently infected with the disease making it the deadliest disease in human history. Giant strides have been made in the treatment of HIV through the introduction of Highly Active Antiretroviral Treatment (HAART).

This is dfined as a combination treatment with at least three antiretroviral drugs including at least one protease inhibitor (PI) (Taffe et al 2002). The introduction of HAART has made a tremendous improvement in the treatment of HIV patients in the developed part of the world. The so-called antiretroviral cocktail, which consists of 3 or more antiretroviral drugs, are able to suppress the virus to a remarkable level. Wherever there is access to HAART, the rate of death has decreased to a significant level. However, these drugs cannot completely remove the virus from the human body and hence the disease cannot be cured.

The main disadvantage of HAART is their price. The antiretroviral cocktail cost about 25 USD per patient per day which is an exorbitant amount to patients in the developing part of the world. Inability of these patients to afford this cocktail enhances the increment in the incidence and the rate of death resulting from HIV/AIDS. Another disadvantage is the side effects experienced by HIV patients from the antiretroviral drugs which have made treatment of HIV infection to become a complicated balancing act between the benefits of durable HIV suppression and the risk of drug toxicity (Hoffmann, Rockstroch and Kamps 2006). Serious side effects that are infrequently encountered by HIV patients are gastrointestinal side effect, Nausea and vomiting, diarrhea, hepatotoxicity, pancreatitis, renal problems, CNS disorder to mention but a few.

The best time to start HAART is still subject to controversy. The risk of AIDS must be weighed against the risks of long-term toxicity and viral resistance. These risks and the realization that eradication cannot be achieved have led to less rigid guideline. The initial "hit hard and early" dogma of 1996, which recommended therapy from the earliest stages of infection, has since been discarded. Also, old idea of treating HIV patients with viral load above 10,000 copies/ml, independent of CD4 cell counts, is similarly no longer a common practice.

Harrington (2000) proposed more appealing new idea (motto) known as “hit hard but when necessary”. There is worldwide agreement that all symptomatic patients as well as patients with less than 200 CD4+ T-cell/µl should be treated.

The high costs of HAART and the frequent, serious side effects have led investigators to explore the possibility of interrupting HAART in a controlled manner (Structured Treatment Interruption, STI). Several studies have been published on patients who stopped HAART and were subsequently carefully followed up. These patients had an undetectable plasma viral load at treatment interruption, but very quickly, plasma HIV RNA levels rose again to pre-treatment levels. In addition, the results of past studies of patients who stopped their treatment show that these patients are worse off in terms of morbidity and mortality than patients who are on continuous treatment. This study focuses on patients who have their treatments interrupted for 3 months or more.

1.3 Research Questions

The research questions for this study were as follow:

1. What are the outcomes of patients with chronic HIV-1 infection who stop their highly active antiretroviral treatment for reasons other than treatment failure, in terms of

i. Rebound of plasma viral loads
ii. Decrease in CD4 cell counts or percentages

2. Which factors are predictive of "good control" of infection (i.e. slow rebound of plasma viral load and slow decrease in CD4 cell counts).

This report is organized as follows; section two describes the data and the study design, section three broadly describes the methodology used in the report which is follow by results of the analysis in section four. In section five, there is detail discussion of results and conclusions arrive at from the analysis while section six contains the list of references for further reading. SAS version 9.1.3, and R are the software used in the analyses presented in this report and all tests are carried out at 5% level of significance.

2.0 The Data

The data used in this study were obtained from the clinical department of the Institute of Tropical Medicine (ITM), Antwerp, Belgium. These data were gathered from a cohort study of patients with chronic HIV-1 infections with age higher than 18 years old and being placed on HAART for at least one year. Also the eligibility criteria specify that the patients should have had undetectable viral load at treatments interruption and have their treatments interrupted for at least 3 months. There were 4 different set of data collected which are *patients data* that consist of patients baseline information like sex, age, sex preference and origin (country of origin). The second one contain different drugs (HAARTS) that each patient is being placed on, next is the *CD4 interruption* which has information on the date at which patients were placed on drug holiday and when they resumed back to drug usage with their respective CD4 counts. It also has information on the date of entry into the study and the last date of visitation to the clinic, these similar information are contained in the fourth dataset which are on patients viral load during interruption (or drug holiday). All these data are merged into two distinct data known as viral load interruption data and CD4 interruption data with full information on the patients and are then used in the analyses considered in this study.

2.1 Definition of Terms

In this study, several variables are used as predictors and therefore have to be explained for proper understanding. These are outcome variables as well as predictor variables which shall be explained in detail in the next subsections. A treatment interruption is refers to as the absence of any antiretroviral drug during at least three months in a patient who was previously receiving HAART.

The end of interruption was defined as the time when the patients start receiving the treatment again, even if it was not with HAART (Taffe et al 2002). Patients were censored when they are observed not to have failed due to high viral load or low CD4 cell counts.

2.1.1 Outcome Variables

The outcome variables used in this report are the time to viral and immunological failures which are:

- rebound of plasma viral load defined as an increase of 100 copies/ml
- decrease in absolute CD4 cell count defined as decrease of 25% compared with baseline value at treatment interruption or a CD4 count < 200/µl

2.1.2 Predictor Variables

Several predictors are considered in this study and they are given in detail in the subsection below

- *Age*: the age of the patients at the start of HAART
- *Sex*: the gender of the patients which can either be male or female as defined in the dataset
- *Sex preference*: the sexual preference of the patients with zero stands for unknown sex preference; 1 stands for bisexual; 2 for homosexual and 3 stand for heterosexual
- *Ethnic origin*: Every patient has a country of origin which are categorized into continent of origin based on the fact that some country have few patients that it may not be easy modeling with such few observation to avoid convergence problem. This variable is classified into 0 = Asia; 1 = South America; 2 = Africa and 3 = Europe. This variable is abbreviated ***continent*** in the report.
- *Disease duration*: the difference between the date when patients start treatment interruption and the date he/she is tested positive of HIV. It is abbreviated as ***trtdur*** in the report.
- *Duration of follow-up*: defined as difference between the date patient start treatment interruption and the date of first consultation. This is abbreviated as ***fulpdur*** in this report.
- *Duration of interruption*: the duration that patient spent in the treatments interruption is also considered as predictor since it can also be a recon factor that predict the outcome. It is refers to as ***intduration*** in the report.
- *CD4nadir*: the lowest CD4 at the start of interruption.
- *CD4HAART*: the CD4 at start HAART.
- *CD4 lab value*: This is the last CD4 before treatment interruption. This is abbreviated as ***labval*** in the report.
- *VLHAART*: the viral load at start HAART.

- *Viral load lab value*: Similar to what is obtained in CD4, it is the last viral load before start treatment interruption and it is abbreviated as ***vlabval***.
- *PATID*: the patient's unique identification number.
- *VLHigh*: This is the highest viral load before starting HAART and always taken to be *VLHAART*.

3.0 Methodology

The background of this report is the analysis of time-to-event. That is, data are related with the individual time elapse in certain situation or state. Example of these kinds of data comes from various fields of study like medicine, biology, engineering, economics, public health etc. The main characteristic of these data is the issue of *censoring* which occurs when the periods of time for some individuals cannot be completely observed. The presence of censoring makes these data unsuitable to analyze with traditional regression method and hence, calls for appropriate or specific techniques and analyses, usually called Survival Analysis (Hosmer (Jnr) and Lemeshow 1998).

Survival analysis consists of a set of specialized statistical techniques used to study response time data. In analyzing such data, the main objects are to determine the length of time interval spent in a state and the transition probabilities from the current state to the entered state (Berenger 2001).

The interest of this statistical tool is mainly focused on two distinguishing features of time data. Firstly, duration times are non-negative values usually exhibiting highly skewed distribution and therefore assumption of normality may be violated. Secondly, the true duration is not always observed or known.

3.1 Censoring and Truncation

The time period confinement for survival data gives rise to considerations specific to survival analysis, censoring and truncation. Censoring arises when survival time of an individual did not extend to the end of the study (Persson 2002). If death from a specific disease is anticipated, death from another source other than disease under consideration is dealt with as censoring, implying an intension of studying death from the specific disease had not the subject died from some other cause (Clayton and Hills 1993). According to Hosmer (jnr) and Lemeshow (1998), a censored observation is one whose value is incomplete due to random factors for each subject.
Censoring can appear in various forms and the most common forms are explained below:

(i) Right Censored: An observation is said to be right censoring if it is recorded from its beginning until a well defined time before its end time. For instance, if a HIV-1 patient is followed until he has a viral load high than 1000 copies/µl and is followed without experiencing this scenario until the end the observation period, and then this patient is known to be right censored. In other words, an observation is said to be right censored if it begins at time t = 0 and terminate before the outcome of interest is observed.

(ii) Left Censored: An observation is said to be left censored if all that is known is that the individual developed the event of interest prior to the beginning of the study. An observation is said to be left censored if the event of interest has already occurred when observation begins (Hosmer (jnr.) and Lemeshow 1998). This situation is less common in survival studies and is often not a focus.

(iii) Interval Censored: An observation is categorized into interval censored if it is only known that the event of interest occurs within an interval of time without the knowledge of when exactly it occurs.

Truncation can be defined as a way to include into a study only those patients who meet certain criteria. One might have left truncation, when only individuals who survive a certain time before the start of the study are included, or right truncation, where the ones who have experienced the event by certain time are included (Persson 2002). In this study, right truncation is used with patients that have already been tested positive to HIV by 2000 being included in the study.

3.2 Analysis of Survival Data

Suppose *X* is the variable describing the event of interest which is known as time taken to some event of interest. There are basically four functions that characterize the variable *X*; *the survival functions, the probability density function, the hazard function and the mean residual life* at time *x*. If one of these functions is known then, the rest can be uniquely determined.

The survival function $S(x)$, is interpreted as the probability that an individual survives for a time greater than or equal to time *x* (Collet 1994). This function can be estimated by the empirical survivor function, given by

$$\tilde{S}(x) = \frac{Number\ of\ individuals\ with\ survival\ times \geq x}{Number\ of\ individuals\ in\ the\ data\ set} \qquad \text{(i)}$$

The estimated *survivor function* $\tilde{S}(x)$ is assumed to be constant between two adjacent death times, and so a plot of $\tilde{S}(x)$ against *x* is a step-function (Collet 1994), the empirical survivor function is equal to unity for values of *x* before the first death time, and zero after the final death time.

The *survival function* is connected to the *probability density function* through the alternative definition of the survival function given as

$$\tilde{S}(x) = 1 - \tilde{F}(x) = p(X \geq x) = \int_x^{\infty} f(t)\, dt \qquad \text{(ii)}$$

Where $\tilde{F}(x)$ is the *empirical distribution function*, that is the ratio of the total number of individuals alive at time *x* to the total number of individuals in the study and subsequently we have

$$f(x) = \frac{dF(x)}{dx} = -\frac{dS(x)}{dx} \qquad \text{(iii)}$$

The *hazard function* is also known as *failure rate, force of infection, force of mortality, conditional failure rate, intensity function, or simply hazard rate* and it is defined as the probability that an individual dies at time *x*, conditional on the fact that he or she has survived to that time. It therefore, represents the instantaneous death rate for an individual surviving to time *x*. For $h(x) \geq 0$, the *hazard ratio* is defined thus:

$$h(x) = \lim_{\Delta x \to 0} \frac{p[x \leq X < x + \Delta x | X \geq x]}{\Delta x} \qquad \text{(iv)}$$

If *x* is continuous, then

$$h(x) = \frac{f(x)}{S(x)} = -\frac{d[lnS(x)]}{dx} \qquad \text{(v)}$$

The *cumulative hazard function* is defined by

$$H(x) = \int_0^x h(u)du = -\ln\,[S(x)] \qquad \text{(vi)}$$

For modeling survival data, a suitable distribution for the survival times is chosen, or equivalently, a hazard functions. This can be achieved in different ways. One way is to assume that the survival time has parametric distribution while another choice is non-parametric where survival times are estimated through the observed survival distribution. The latter is the basis for Kaplan-Meier which is considered in the next subsection. There is semi-parametric approach in which one does not specify any distribution apart from assuming *hazard function* changes in steps which occur at the observed event. This is the basis for *Cox-proportional hazard* model (Olsson 2002).

3.3 Estimate of Survivorship Function

The repercussions of the time confinement employed when collecting survival data are censoring and truncation. The differences in survival experience between two groups receiving different treatments can be tackled from different angles; often times, a researcher will be interested in how long an individual of certain age will live or perhaps how long after the exposure will the disease occur; the incubation period. In addition, to these aims, traditional statistical methods do not suffice, instead there are whole arsenal of methods developed solely for purposes of estimation of various angles of approach to survival data taken censoring and truncation into account.

3.3.1 The Non-Parametric Kaplan-Meier Product Limit Estimates

The Kaplan-Meier estimator estimates the survival function from life-time data. In medical or biological research, it might be used to measure the fraction of patients living for a given amount of time after surgical operation. A plot of this estimate of the survival function is a series of horizontal steps of declining magnitude which, when a large enough sample is taken, approaches the true survival function for that population. The value of the survival function between successive distinct sampled observations is assumed to be constant. One way to measure survival is to make use of actual survival times confined to a certain interval of time. Cumulative survival is then estimated as the proportion of survivors among these patients over these intervals of time. One major advantage of Kaplan-Meier estimates is that the method can take into account "censored" data. That is, since it look unwise to overlook the survival experience of patients with whom one loses contact and the more recently recruited patients who have not yet completed their entire follow-up time. The simple cohort-based methods have been modified to take these patients into consideration. The result is called complete method and the most widely used complete method is called Kaplan-Meier survival estimator.

3.3.1.1 Comparison of Survival Curves Using Different Methods

In medical research, it is often the case to compare the survival curves of two groups of individuals. The groups will defer with respect to a certain (prognostic) factor like *treatments*, *age*, *sex*, *stage of disease*, etc., and it is the effect of this factor on survival which is of interest. The simplest way of comparing survival time obtained from two groups of individuals is to plot the corresponding estimates of two *survivor functions* on the same axes (Collet 1994). However, this is an exploratory method which may not be concluded upon, and hence, the need for formal statistical method to assess whether the two groups are different with respect to their survival time. In the comparison of two groups of survival data, there are a number of methods which can be

used to quantify the extent of between-group differences. Two non-parametric approaches that are commonly used in practice are *log rank test* and *Wilcoxon test.*

3.3.1.2 The Log-Rank Test and Wilcoxon Test

The log-rank test (also called the Mantel-Haenszel test or Mantel-Cox test) is a hypothesis test to compare the survival distributions of two samples. It is a non-parametric test and appropriate to use when the data are right censored (technically, the censoring must be non-informative). The log-rank test statistic compares estimates of the hazard functions of the two groups at each observed event time. It is constructed by computing the observed and the expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all time points where there is an event (Hosmer (Jnr) and Lemeshow 1998).

Let j be the number of distinct times of events. For $j = 1, \ldots, J$, and let O_j be the observed number of events in the first group, let E_j *and* V_j respectively be the expected value and variance of O_j given the number of events at this time *and the number* of patients "at risk" (neither censored nor had event) in both groups under the null hypothesis. O_j conditionally has a hypergeometric distribution. E_j is the number of events times the fraction of the total number at risk that are in group 1. That is, from sample;

$$e_{1j} = \frac{n_{1j} d_j}{n_j} \qquad \text{(ix)}$$

so that e_{1j} is the expected number of individual who die at time t_j in group 1. Taking o_{1j} as d_{1j}, then the deviation between the expected death and the observed death from 2 x 2 tables constructed for each event time is then combined and given as;

$$U_L = \sum_{j=1}^{r} \left(d_{1j} - e_{1j}\right) \qquad \text{(x)}$$

Since death times are independent of one another, the variance of U_L is simply the sum of the variances of d_{1j}. Now since d_{1j} has a hypergeometric distribution, the variance of d_{1j} is given as;

$$v_{1j} = \frac{n_{1j} n_{2j} d_j (n_j - d_j)}{n_j^2 (n_j - 1)} \quad \text{and} \quad \text{var}(U_L) = \sum_{j=1}^{r} v_{1j} = V_L \qquad \text{(xi)}$$

U_L is considered to be approximately normally distributed, when the number of 'death' is not too small (Collet 1994). It then follows that $U_L / \sqrt{V_L}$ has a normal distribution with mean zero and unit variance, denoted as *N(0,1).* We therefore write

$$Z = \frac{U_L}{\sqrt{V_L}} \sim N(0,1) \quad \text{(xii)}$$

Therefore the square of a standard normal random variable has a chi-square distribution on one degree of freedom and so we have

$$Z^2 = W_L = \frac{U_L^2}{V_L} \sim \chi_1^2 \quad \text{(xiii)}$$

Where W_L implies Wald test.

Because this approach of combining information over several 2 x 2 tables was proposed by Mantel and Haenszel (1959), it is then called Mantel-Haenszel procedure. The test based on this statistic has several names, including *Mantel-Cox* and *Peto-Mantel-Haenszel*, but it is probably best known as *log-rank test.* The test is known to have high power when the proportional hazard model holds.

The *Wald statistic* summarizes the extent to which the observed survival times in the two groups of data deviate from those expected under the null hypothesis of no group difference. The larger the value of this statistic, the greater the evidence against the null hypothesis.

This test can be generalized to accommodate other tests that are equally used sometime in practice such as *Generalized Wilcoxon test, Tarone-Ware test, and Peto-Peto Prentice test.* Each of these tests uses different weight to adjust for censoring that is often encountered in survival data. Suppose that our U_L *is defined* as;

$$U_L = \sum_{j=1}^{r} w_j\left(d_{1j} - e_{1j}\right) \quad \text{(xiv)}$$

and

$$var(U_L) = \sum_{j=1}^{r} w_j^2 v_{1j} = V_L \quad \text{(xv)}$$

Then W_L is as defined in equation *xiii*

When the weight is 1, we have *log-rank test, generalized Wilcoxon* test uses weights equal to the number at risk which puts relatively more weight on the differences in survivorship function at smaller values of time. The log-rank test will place more emphases on differences in survivor function at larger values of time than generalized Wilcoxon test since it makes use of weight equals 1. Tarone and Ware (1977) suggested assigning weight that is intermediate between *log-rank and generalized* Wilcoxon and hence proposed $w_j = \sqrt{n_j}$. On the part of Peto and Peto (1972) and Prentice (1978), they suggested using a weight function that depends more explicitly on the observed survival experience of the combined sample. The weight is then given as

$$w_j = \tilde{S}(t_{j-1}) \times \frac{n_j}{n_{j+1}} \qquad \text{(xvi)}$$

Harrington and Fleming (1982) suggested a class of test that incorporates features of both log-rank and the Peto-Prentice tests. They suggested using the Kaplan-Meier estimator raised to a power, as the weight, namely

$$w_j = [S(t_{j-1})]^{\rho} \qquad \text{(xvii)}$$

When ρ = 0 then, $w_j = 1$ and the test is the *log-rank test*. However, if ρ = 1, then the weight is the Kaplan-Meier estimator at the previous survival time, a weight similar to that of Peto and Prentice test. The principle advantage of Peto-Prentice and Harrington-Fleming tests over the generalized Wilcoxon test is that they weight relatively to the overall survival experience.

A problem can occur if the estimated survivorship functions cross one another. This implies that in some time interval, one group will have a more favorable survival experience, while in other time intervals the other group will have the more favorable experience (Collet 1994). This is similar to having interaction present when applying Mantel-Haenszel method to a stratified contingency table.

3.4 Regression Models for Survival Data

In most medical studies which give rise to survival data, supplementary information is collected on each individual so that the relationship between the survival experience of individuals and various explanatory variables may be investigated. A variety of models and methods have been developed for doing this sort of survival analysis – some parametric and some semi-parametric. Semi-parametric models are models that parametrically specify the functional relationship between the lifetime of an individual and his characteristics (demographic, socio-economic, etc.) but leave the actual distribution of lifetimes arbitrary. The most popular of the semi-parametric models is the *proportional hazards model,* which has the property that ratio of the hazards of two individuals at time *t* can depend on the values of their explanatory variables, say $x_1, x_2, \ldots\ldots$ but does not depend on time *t*.

3.4.1 The Semi-Parametric Cox-Proportional Hazard Model

Sir David Cox (1972) proposed a distribution-free (semi-parametric) proportional hazards model to cater for covariate effects for single event failures (lifetime data) in a non-repairable system. This model is valid under the assumption of proportional hazards which implies that effect parameters multiply hazards, for instance, if taking drug *X* halves your hazard at time 0, it also halves your

hazard at time 1, or time 0.5, or time *t* for any value of *t*. Cox (1972) observed that if proportional hazards assumption holds (or is assumed to hold), then it is possible to estimate the effect parameter(s) without any consideration of the hazard function.

The Cox proportional hazards model is generally given by;

$$h_i\left(t\middle|Z_j(t)\right) = h_0(t)exp\left(Z_j(t)'\boldsymbol{\beta}\right) \qquad \text{(xviii)}$$

where $h_0(t)$ is the baseline hazard function at time *t*, $Z_j(t)$ is a vector of measured covariates for the i^{th} individual at time *t*, and **β** is a vector of unknown regression parameters that are assumed to be the same for all individuals in the study. The data available in regression problems for right-censored time data are independent observations on the triple (*X*, *ð*, ***Z***), where *X* is the minimum of death and censoring time pair (*T*, *U*), $\delta = I_{T\leq U}$ is the indicator of whether or not a 'death' has been observed (censoring indicator), and $\boldsymbol{Z} = (Z_1, Z_2, \ldots, Z_p)^1$ is a *p* dimensional column vector of covariates. The vector ***Z*** may be a function of *t*, but the only requirement is that ***Z(t)*** can be determined from the observations up to time *t*.

The Cox proportional hazards model can equally be regarded as linear model for the logarithm of the hazard ratio given by

$$log\left\{\frac{h_i(t)}{h_o(t)}\right\} = Z_j(t)'\boldsymbol{\beta} \qquad \text{(xix)}$$

From this hazard function, we obtained estimated cumulative hazard function and given by:

$$\hat{H}_i(t) = exp\left(Z_j\hat{\boldsymbol{\beta}}'\right)\hat{H}_0(t) \qquad \text{(xx)}$$

Consequently, from the proportional hazard function, we obtained the estimated survivor function for the *ith* individual which is given by:

$$\hat{S}_i(t) = \left[\hat{S}_o(t)\right]^{exp\left(z_j\hat{\beta}'\right)} \qquad \text{(xxi)}$$

for $t_k \leq t \leq t_{(k+1)}$, $k = 1,2,\ldots,r-1$, with *r* set of observed death time (Collet 1994).

The explanatory variables included in the model might be covariates which are assumed to be continuous such as *age*, *height*, *weight*, and so on, or factor(s) which are in categorical form such as *sex* (with male = 0,, female = 1), *disease stage* (stage1 = 0, stage2 = 1, etc.), and so on. In estimating factor variables in the model, for instance, if factor *A* has a levels, *(a-1)* dummy

variables have to be created, each has two levels 0 or 1 indicating the presence of a level or not. In addition, an interaction term may be needed in a model. This is often the case when terms corresponding to more than one factor are to be included in the model, sets of indicator variables can be defined for each factor in a manner that each dummy variable created has two levels, 0 or 1. In this situation, it may be appropriate to include a term in the model which corresponds to effects for each combination of levels two or more factors. Such effects are known as interaction (Collet 1994).

3.4.2 Parametric Proportional Hazards Models

Other proportional hazards models exist in form of parametric which assume that the proportional hazards assumption holds, but in addition, assume that the hazard function follows a know form. There are two major form of this parametric hazard model that are commonly used in practice known as *Exponential* and *Weibull* models for survival data.

The Exponential and Weibull Models for Survival Data

The simplest model for the hazard of an event of interest is to assume that it is constant over time. The hazard of experiencing event of interest at any time after the time origin of the study is then the same, irrespective of the time elapsed. The estimated hazard and survivor functions under this model which is assumed to follow exponential distribution are obtained and given respectively by;

$$h(t) = \lambda(t) \qquad \text{(xxiia)}$$

and

$$\hat{S}(t) = exp(-\lambda(t)) \qquad \text{(xxiib)}$$

In practice, the assumption of a constant hazard function, or equivalently of exponentially distributed survival times, is rarely tenable (Collet 1994). Therefore a more general form of estimated hazard function is such that

$$\hat{h}(t) = \hat{\lambda}\hat{\gamma}t^{\hat{\gamma}-1}, \qquad \text{(xxiic)}$$

for $0 \leq t \leq \infty$ and with corresponding estimated survivor function given by;

$$\hat{S}(t) = exp\left(-\hat{\lambda}(t)t^{\hat{\gamma}}\right) \qquad \text{(xxiii)}$$

where λ is Weibull's scale parameter and γ is its shape parameter. This model assumed that the survival times of *n* individuals are now taken to be a censored sample from a Weibull distribution. The two parameters are estimated using maximum likelihood which are obtained by differentiating log likelihood with respect to each of these parameters and solve the nonlinear equations resulted from the differentiations to obtain the estimate of the parameters.

In comparing two groups using the Weibull distribution model, under the proportional hazards model, the estimated hazard of death at time *t* for individual *i* is given by;

$$\hat{h}_i(t) = exp\left(\hat{\beta}_1 z_{1i} + \cdots + \hat{\beta}_j z_j\right)\hat{\lambda}\hat{\gamma}t^{\hat{\gamma}-1} \qquad \text{(xxiv)}$$

The estimated hazard function for individuals in group 1 is given as we have in equation xxviii by;

$$\hat{h}_0(t) = \hat{\lambda}\hat{\gamma}t^{\hat{\gamma}-1} \qquad \text{(xxv)}$$

We hence have result that if the survival times of individuals in one group have a Weibull distribution with shape parameter γ, and the hazard of event of interest at time *t* for an individual in the second group is proportional to that of an individual in the first group, the survival times of those in the second group will also have a Weibull distribution with shape γ. This distribution is then said to have a *proportional hazards property*. When assuming the proportion hazards function to be the *Weibull*, hazard function gives the *Weibull proportional hazards model* (in which the survival times follows a Weibull distribution). The estimated survivor function for the i^{th} individual in the study is given by;

$$\hat{S}_i(t) = exp\left\{-exp\left(z_{1i}\hat{\beta}_1 + \cdots z_{ji}\hat{\beta}_j\right)\hat{\lambda}t^{\hat{\gamma}}\right\} \qquad \text{(xxvi)}$$

3.4.3 Analysis of Interval – Censored Data

Both parametric and non-parametric methods are available for the analysis of interval censored data when observations are assumed to be independent (Bellamy et al 2004). In this study, analysis of interval-censored data is done using conventional interval-censored data analysis methods implemented in some popular software like SAS, STATA, and R/S-Plus. With interval-censored data, instead of T_i *(i = 1, . . ., n),* a random variable recording the duration time of the ith patient in the study, we observe intervals $[L_i, R_i]$, where $L_i \leq T_i \leq R_i$. This does not rule out exactly observed, right-censored, left-censored data for which $L_i = R_i = T_i$, $R_i = \infty$ and $L_i = 0$, respectively. Often, additionally a vector x_i of covariates (*i =1, . . ., n*) with typical question of whether the distribution of T_i relies on the covariates (Lessafre et al. TR068).

In the method of analyzing interval-censored survival data, information about whether or not viral failure occurs at different examination schedules is taken into account. Adopting a proportional hazards model for the recurrence times, the hazard of experiencing viral failure at time t_j in the i^{th} individual can be expressed as

$$h_i(t_j) = exp\left(Z_j\beta'\right)h_0(t_j) \qquad \text{(xxvii)}$$

Where $h_0(t)$ is the baseline hazard at time t_j, and ($\mathbf{Z_j\beta}$) is the risk score for the i'th individual. This assumption is less restrictive to the one obtained in Cox-proportional hazard model because it only assumes that hazards need only to be proportional at the schedule time t_j, and not at intermediate times. Corresponding survivor function for interval-censored data can be obtained from the hazard function given as

$$log\{-log(1-\pi_{ij})\} = Z_j\beta' + log[-log\{S_0(t_j)/S_0(t_{j-1})\}] = Z_j\beta' + \gamma_j \qquad \text{(xxiii)}$$

This is a linear model for complementary log-log transformation of π_{ij}, in which γ_j, j = 1, 2, . . .,k are associated with the k time intervals. The model is fitted using standard method for binary data which is similar to fitting logistic regression and assessment of model inadequacy that are applicable to logistic regression are also applicable to this interval-censored analysis.

3.4.4 Model Building

Before any model could be fitted, it is a statistical tradition to investigate which variable(s) goes into the model either by using conventional selection procedure like forward, backward, stepwise which are in a class of automatic selection procedures or follows a specific intuition that is statistically acceptable. Model building in Survival analysis is similar to what is obtained in a classical regression (Hosmer (Jnr) and Lemeshow 1998). Any of the standard approaches describe in any statistical text can be adopted in selecting the variables that goes into final model because they are likelihood based ad because standard testing procedures like the score test can be used to compare models except if there is (are) specific variables that need to be forced into the model because of its biological interest.

In this study, model building starts from univariate analysis as suggested by Collet (1994). All variables that are significant at 25% level from one explanatory univariate regression model are taken into multivariable model where backward selection approach is used with 10% significant level of stay in the model. Variables that are selected at this stage are taken to stage three where variables that are not significant in stage one are added one at a time and forward selection procedure is used with 10% significant level of entry into the model. The fourth stage involves combination of all variables that are significant at stage three in addition with their possible interactions using stepwise selection procedure with 10% significant level of entry and stay in the model. The final variables selected at this stage are then pruned to have the final model.

3.5 Assessment of Model Adequacy

Model-based inferences depend completely on the fitted statistical model. For these inferences to be "valid" in any sense of the word, the fitted model must provide an adequate summary of the data upon which it is based. Some of the methods for the assessment of a fitted proportional hazards model can equally used for parametric regression models. There are basically four requirements for model adequacy considered in this study. They are (i) methods for testing the assumption of proportional hazards. This is an assessment of how extent the two curves are equidistant over time. (ii) Goodness-of-fit can be assessed using R^2 similar to what is obtained in linear regression proposed by Cox and Snell (1989) and given by

$$R^2 = 1 - exp\left[\frac{2}{N}\left(LL_0 - LL_{\hat{\beta}}\right)\right] \qquad \text{(xxx)}$$

where LL_0 is the (partial) log likelihood for zero model, LL_β is the (non) parametric model as appropriate, N is the number of time-intervals in the event sequence (Klein and Moeschberger 2003). (iii) Subject-specific diagnostic statistics that extends the notions of leverage and influence to the proportional hazards model and (iv) testing for non-linearity in Cox-Proportional regression model (Hosmer & Lemeshow 1998).

Under this model adequacy, residuals play a central role. The following residual diagnostics are considered in assessing model adequacy in this study; (i) Scale Schoenfeld residuals which is expected to show no trend in addition to its smooth plot if the proportional hazard assumption is satisfied, (ii) the score residual which is a weighted average of the distance of the value, $z_{ij,}$ to the risk set means, z_{wjk}, with the weights taken as the change in the martingale residual, that is used in assessing subject-specific diagnostic by observing how large the deviation is. The larger the deviation the more distant the residual is to the mean. (iii) Martingale residual proposed by Hosmer (jnr) and Lemeshow (1989) to assess goodness-of-fit by partitioning the data into G groups based on the ranked values of the estimated risk score, $z'\boldsymbol{\beta}$. The test sums up the martingale residuals within each group and it compares the observed number of events in each group to the model-based estimate of the expected number of events (Hosmer (Jnr) & Lemeshow 1998).

4.0 Results

4.1 Exploratory Data Analyses

In exploring the data, we make use of descriptive statistics for the continuous variables and frequency tables for categorical variables. In addition, chi square test in form of Fisher's exact test or Pearson Chi-square is used in assessing if the categorical variables are independent of each

other or not whereas t-test with assumption of normality is used to compare categorical variables with only two levels and *general linear model* for categorical response variables with more than two levels. Variables are summarized using descriptive statistics is with respect to age, sex, sex preference, and continent of origin. Graphical illustrations are also used to visually assess the level of each variables considered in this study. Some of the graphical displays are histogram, box plot and bar-charts.

4.1.1 Missingness Assessment

In these data, there are some missing observations in some of the covariates that call for attention. We investigate the proportion of missingness in these covariates before proceeding to the analysis. From Table 1, we found that for highest viral load before starting HAART, there is 57% missingness, whereas there is 19% missingness in the highest CD4 before starting HAART. We decided to include variables that are having less than 30% missingness in the analysis to avoid loosing much information in the analysis, though we observe that this is going to have influence in the analysis since information will be lost on some of the patients in the dataset. The missing data, as observed from the software, are handled by using complete case in fitting the proposed models. The influence of missing observations on the results shall be investigated in due course. The following variables are not included in the analysis due to their high proportion of missingness: *vlhaart* and *Vlhigh*.

Table 1: Distribution of missingness in the viral load and CD4 data for patients with chronic HIV-1 infection who interrupt their highly antiretroviral treatments at ITM, Antwerp, Belgium

Variable	***Number of missing***	***Percentage of missing***
CD4haart	28	19%
Vlhaart	82	57%
Vlhigh	82	57%

4.1.2 Descriptive Statistics

There are 1296 patients in the cohort study out of which 148 patients have their treatment interrupted not due to treatment failure and 1148 are without drug holiday. The mean age of those that have treatment interruption is 36 years while mean age of those without treatment interruption is found to be 37 years. The box plot shown in Figure 1 (left panel) shows that there is relatively little difference in the age distribution of the two groups. The statistical t-test confirms that there is no significant difference between the age of patients with treatment interruption and those without interruption (p-value = 0.1506). There are 876 males in the study out of which 94 (11%) are in the

treatment interruption category and 782 (89%) are in the non-interruption group. Among 419 females in the study, there are 54 (13%) in interruption arm and 365 (87%) in non-interruption. Figure 1 (panel b) shows the bar-chart that depicts the sex distribution according to patients' situation in the study.

Considering the distribution of patients' situation according to continent of origin shows that there are 37 (3%) patients from Asia out of which 1 is being classified into treatment interruption arm and 36 are classified into non-interruption arm. South America records a total of 18 (1%) patients that have 3 patients in interruption category and 15 in non-interruption category. Similarly, there are 433 (33%) patients from Africa with 42 in interruption arm and 391 in the other arm. This continent recorded second largest number of patients in the study. The highest percentage of patients comes from Europe, which has a total of 808 (62%) patients in the study with 102 are among those patients who have their treatments being interrupted and 706 are not. The information presented above is presented graphically in Figure 3 (rigt panel) in the Appendix and in Table 1. The remaining descriptive statistics focuses on patients with treatments interruption, while the information about both groups can be found in Table1. The average age of females in this arm is 34years while the average age of males is 37years. Figure 3 (left panel) in the appendix shows the box plot of age against sex. This plot shows that there is difference between average age of male and that of the female patients in the study. This can be observed clearly from the plot through the mean level. The mean level in the box plot for male is higher than that of the female. However, a formal test using t-test reveals that there is no significant difference between the gender (p-value = 0.1719).

Age Distributions

Age distribution in terms of *continent of origin* (Table 1) reveals on the one hand that the mean ages of patients from South America, Africa, Asia and Europe, who have their treatment interrupted, are respectively 38, 33, 38, and 37years. On the other hand, the mean age of patients who are not on drug holiday from the aforementioned continents are respectively 31 years, 35 years, 34 years and 39 years. Statistical test for age difference in the *continent of origin* among patients with interruption using GLM shows that there is no significant difference among the age distributions of the patients (p-value = 0.0506). However, for patients without interruption, we observed that there is high significant difference in the age distribution according to the continent of origin (p-value < 0.0001). Bar-chart illustrating these distributions is shown in Figure 3.

Table 2: Descriptive statistics of chronic HIV-1 patients who interrupt their highly active antiretroviral treatment (HAART) data obtained at ITM, Antwerp, Belgium

	Patients with interruption			**Patients without interruption**		
	N (%)	*Mean (st.dev)*	*normality test*	*N (%)*	*Mean (stdev)*	*Normality test*
Age	148 (11.4%)	36 (8.85)	< 0.0001	1148 (89%)	37 (9.65)	< 0.0001
t-test for group difference (p-value = 0.1506)						
Sex						
	N (%)	*Mean (st.dev)*	*t-test/ GLM*	*N*	*Mean (stdev)*	*t-test/GLM*
Male	94 (64%)	37 (8.8)	0.0323	782 (68%)	39 (9.7)	< 0.0001
Female	54 (36.5%)	34 (8.6)		366 (32%)	33 (8.6)	
Continent of origin						
Asia	1(0.7%)	38 (-)	0.0510	36 (3%)	31 (6.03)	<.0001
S.America	3 (2.03%)	38 (13.9)		15 (1.3%)	33.5 (7.8)	
Africa	42 (28.4%)	33 (8.4)		392 (34%)	33 (7.8)	
Europe	102 (69%)	37 (8.69)		706 (61.5%)	39 (10.0)	
Sexual Preference						
unknown	1 (0.7%)	32 (-)	<0.4901	12 (1.04%)	38 (13.4)	< 0.0001
Bisexual	2 (1.4%)	41 (4.24)		31 (2.7%)	42 (10.96)	
Homosexual	60 (40.5%)	35 (7.2)		476 (41.4%)	38 (9.3)	
Heterosexual	85 (57.4%)	37 (9.9)		630 (54.8%)	36 (9.6)	

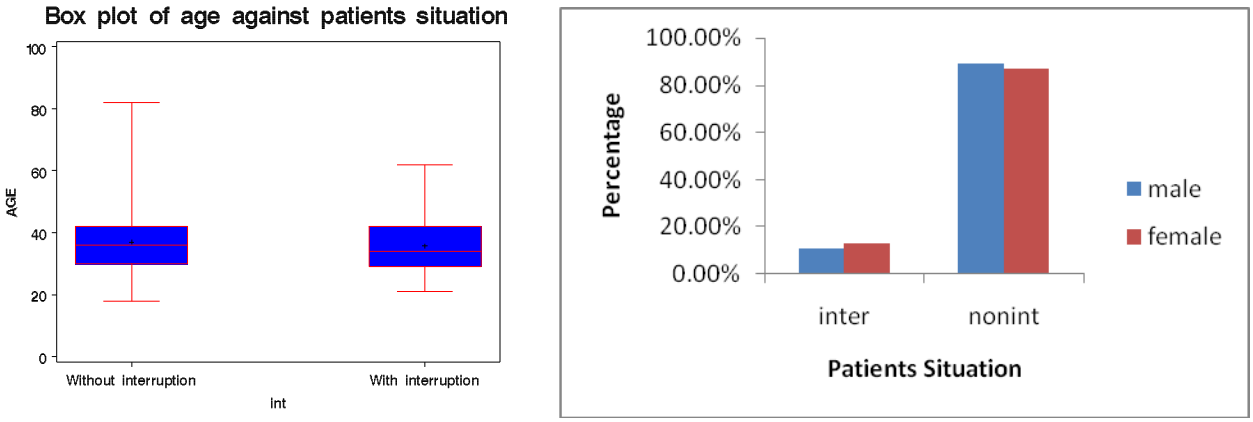


Figure 1: Box plot showing age distribution between patient with interruption and without interruption (left panel) and bar-chart showing percentage of sex according to patients' situation(right panel)

The age distribution of patients with interruption of their treatments is skewed to the right. From this graph, it shows that there are more young people than older people in the study. Similar observation is made from the age distribution of the patients without interruption in their treatments. This can be clearly observed from Figure 2 (right panel).

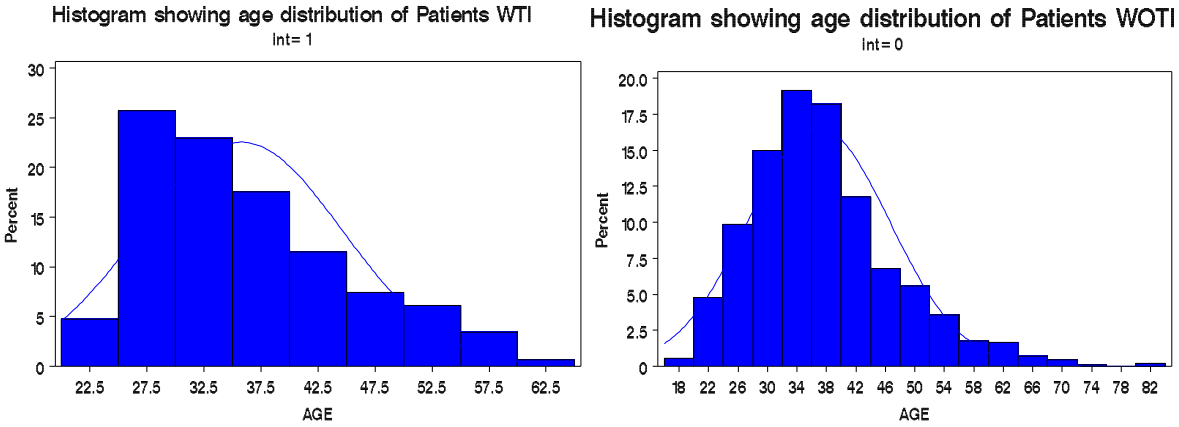


Figure 2: Histogram showing age distribution of patients with interruption (left panel) and without interruption (right panel) from chronic HIV-1 infected patients at ITM, Antwerp, Belgium

In addition, distribution of *sex* in terms of *continent of origin* from patients who have their treatment interrupted shows that there are 29 (19.6%) females from Africa whereas there are only 24 (16.2%) from Europe in general. These two continents account for largest proportion of females in the group. South America accounts for only 1 female patient while no female patient is recorded for Asia continent. In terms of male participants, there are more males reported from Europe (78 (52.7%)) against Africa (13 (8.8%)). There are 2 (1.4%) male patients from South America and 1(0.7%) male patient from Asia. Fisher's exact test shows that there is an association between *continent of origin* and *sex* with p-value < 0.0001. In general, there are 102 (68.3%) patients from Europe, 42 (28%) patients from Africa, 3 (2%) from South America and 1(0.7%) from Asia in this study. The distribution is similar with what we observed in non-interruption group. This is displayed in Table 2 for detailed information about the group. Chi-square test shows that there is significant association between sex and continent of origin in both groups (p-value < .0001).

Table 3: Distribution of sex and sex preference according to continent of origin for data obtained from chronic HIV-1 patients who interrupt their highly active antiretroviral treatments at ITM, Antwerp, Belgium

Continent of Origin								
Continent (%)	***With interruption***				***Without Interruption***			
	Female	***Male***	***Total***	***Exact-test***	***Female***	***Male***	***Total***	***Exact test***
Asia	0 (0%)	1 (0.1%)	1 (0.1%)	< 0.0001	21 (1.6%)	14 (1.1%)	35 (2.7%)	< 0.0001
South America	1 (0.1%)	2 (0.2%)	3 (0.2%)		3 (0.2%)	12 (0.9%)	15 (1.2%)	
Africa	29 (2.2%)	13 (1%)	42 (3.2%)		245 (19%)	147 (11.3%)	392 (30%)	
Europe	24 (1.9%)	78 (6%)	102 (7.9%)		97 (7.5%)	609 (47%)	706 (54.5%)	
Sex Preference								
Unknown	0 (0%)	1 (0.1%)	1 (0.1%)	< 0.0001	3 (0.2%)	9 (0.7%)	12 (0.9%)	< 0.0001
Bisexual	0 (0%)	2 (0.2%)	2 (0.2%)		1 (0.1%)	30 (2.3%)	31 (2.4%)	
Homosexual	0 (0%)	60 (4.6%)	60 (4.6%)		8 (0.6%)	467 (36%)	475 (36.6%)	
Heterosexual	54 (4.2%)	31 (2.4%)	85 (6.6%)		354 (27.3%)	276 (21.3%)	630 (48.6%)	

Sex by Sex Preference

Analysis of sex by sex preference shows that all the 54 female participants in treatment interruption are heterosexual. However, among males, 60 patients are homosexual while 31 patients are heterosexual. 2 male patients are having bisexual and the *sex preference* of 1 patient is unknown. The test of association (i.e. Fisher's exact test) indicates that there is an association between sex preference and gender (p-value < 0.0001). Similarly, we found that there is uneven distribution of sex according to sex preference in non-interruption group with 7 male patients are of unknown sex preference; 30 are bisexual; 467 male patients are practicing homosexual and the remaining 276 male patients are heterosexual. For female, a clear indication emerges from the distribution which reflects that 353 patients are heterosexual; 8 are homosexual; 1 has bisexual preference while there are two patients with untraced sexual preference. This is shown in Figure 3 using bar – chart to illustrate the distribution for the two groups.

Analysis of *sex preference* according to *continent of origin* shows that 42 patients from Europe are heterosexual, 58 patients are homosexual, 1 is bisexual and 1 is of unknown sexual preference. Also, 41 patients from Africa are found to be heterosexual, none is homosexual and 1 patient is known to be bisexual. Only 1 patient from Asia is found to be homosexual whereas from South

America, 2 patients are found to be heterosexual and 1 patient is found to be homosexual. In the same vein, Fisher's exact test confirms that there is significant statistical association between *sex preference* and *continent of origin* (p-value <0.0001). Table 4 and Figures 3 and 4 provide the details about this information.

Table 4: Distribution of Sex preference according to sex by patients' situation for patients with chronic HIV-1 infection who interrupt their highly active antiretroviral treatments at ITM, Antwerp, Belgium

Continent	***With interruption***					***Without Interruption***				
	0	1	2	3	Exact-test	0	1	2	3	Exact-test
Asia	0	0	1	0	< 0.0001	1	2	10	23	< 0.0001
South America	0	0	1	2		0	0	10	5	
Africa	0	1	0	41		3	1	16	372	
Europe	1	1	58	42		8	28	440	630	

0 = unknown; 1 = Bisexual; 2 = Homosexual; 3 = Heterosexual

From Figures 3 and 4, we observed that there are more male in both bisexual and homosexual classes than female patients but there are more female in heterosexual class than male counterpart. These observations are similar in the two groups (i.e. both with and without interruption).

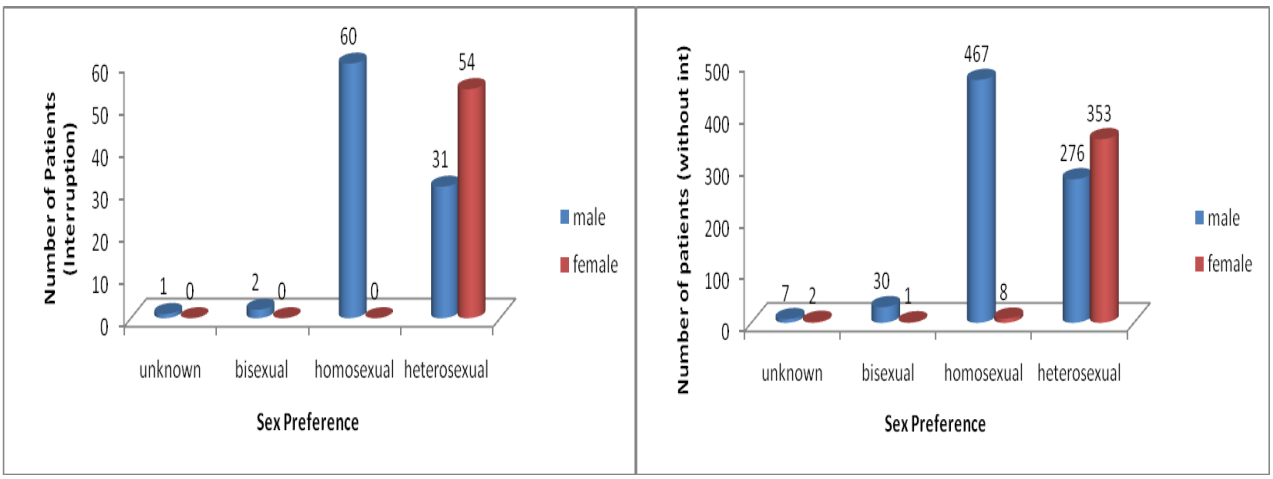


Figure 3: Bar-charts showing the number of patients with respect to sex preference for patients with chronic HIV-1 infection with(left panel) and without (right panel) treatments interruption at ITM, Antwerp, Belgium

4.2 Survival Analysis of Viral Load Data

From these data, in order to be able to carry out right-censored survival analysis, although we are not analyzing *survival* rather we are focusing on *failure time*. Meanwhile, the 'Survival time' used in this report is referring to failure time. The data are structured to have one observation per patient instead of multiple observations recorded per patient due to the timing of viral load measurement experienced by patients during the treatments interruption. The whole dataset are used for interval-censored survival analysis that shall be dealt with later in this study.

The Kaplan Meier survival Plot, Figure 4 indicates that the failure time of patients with viral load less than 1000 copies/ul is small. This is indicated by the median failure time to be 3 months (95 % CI, 2 – 5 months). The 75th percentile is found to be 4 months (95% CI, 3 – 5 months), while 25th percentile is estimated to be 1 month (95% CIs, 1 – 2 months). The plot shows that there are more events at an early part of interruption time which implies that there are more patients who have their viral load more than 1000 copies/ul and these is gradually going down as interruption time is increasing. The end-point in this case is time to viral load failure i.e. having viral load rebound above 1000 copies/µl.

4.2.1 Comparison of Sex, Sex Preferences and Continent of Origin

In order to investigate if there is significant difference between the time to viral failure of sex, Kaplan-Meier survivor estimates are differently estimated for the group and their plots are overlaid so that the difference, if it exists, can be visually investigated. Figure 4 shows that the curves are not much different from each other indicating that the time to viral failure for the male and female patients may not be different significantly. Statistical confirmation is made by using log-rank test and this shows that there is no statistical significant difference between the gender with respect to time to viral failure (Chi-square = 0.1 at 1 d.f., p-value = 0.5542). The median survival time for female and male patients is 2 months, (95% CI, 2 – 3 months).

Similar information is investigated from patients' sex preference if there is any difference worth noting from the data. From Figure 4, we found that for unknown sex preference, and bisexual sex preference, there seem to be early event in great number which may be due to few patients in these classes, for the homosexual and heterosexual patients, it indicates that graphically, there is little difference in their curves. The median time to viral failure for both homosexual and heterosexual patients who have their treatments interrupted is found to be 2 months (95% CI, 1 – 3 months). Using log-rank test to investigate the difference statistically shows that there is no significant

difference in the failure time of the sex preference groups, (Chi-square = 3.282, d.f. = 3, p-value = 0.35).

Similar analysis is performed for *continent of origin* to investigate differences in their time to viral failure among the different continents. Based on the fact that there are very few patients recorded for Asia and South America, observation from the Kaplan-Meier curves shows that these patients quickly experience the event, however, the interpretation should be taken with caution based on the fact that there are few patients from these continents. Considerable number of patients is recorded for both Africa and Europe. Therefore, we use the information provided by the Kaplan-Meier "survival" estimate and log-rank test to conclude on the differences. The null hypothesis is that there is no significant difference between the times to viral failure for the four continents. The curves overlap each other indicating that there may not be any serious difference in the Kaplan-Meier curves for African and Europe indicating that time to viral failure may be the same for the two continents and therefore, there may not be evidence against the null. The median failure time for Africa and Europe each is estimated to be 2 months (95% CI, 2 – 3 months). Log-rank test shows that there is no evidence against the null hypothesis of no difference in failure time with Chi-square value of 2.6077 at 3 degrees of freedom (p-value = 0.4561).

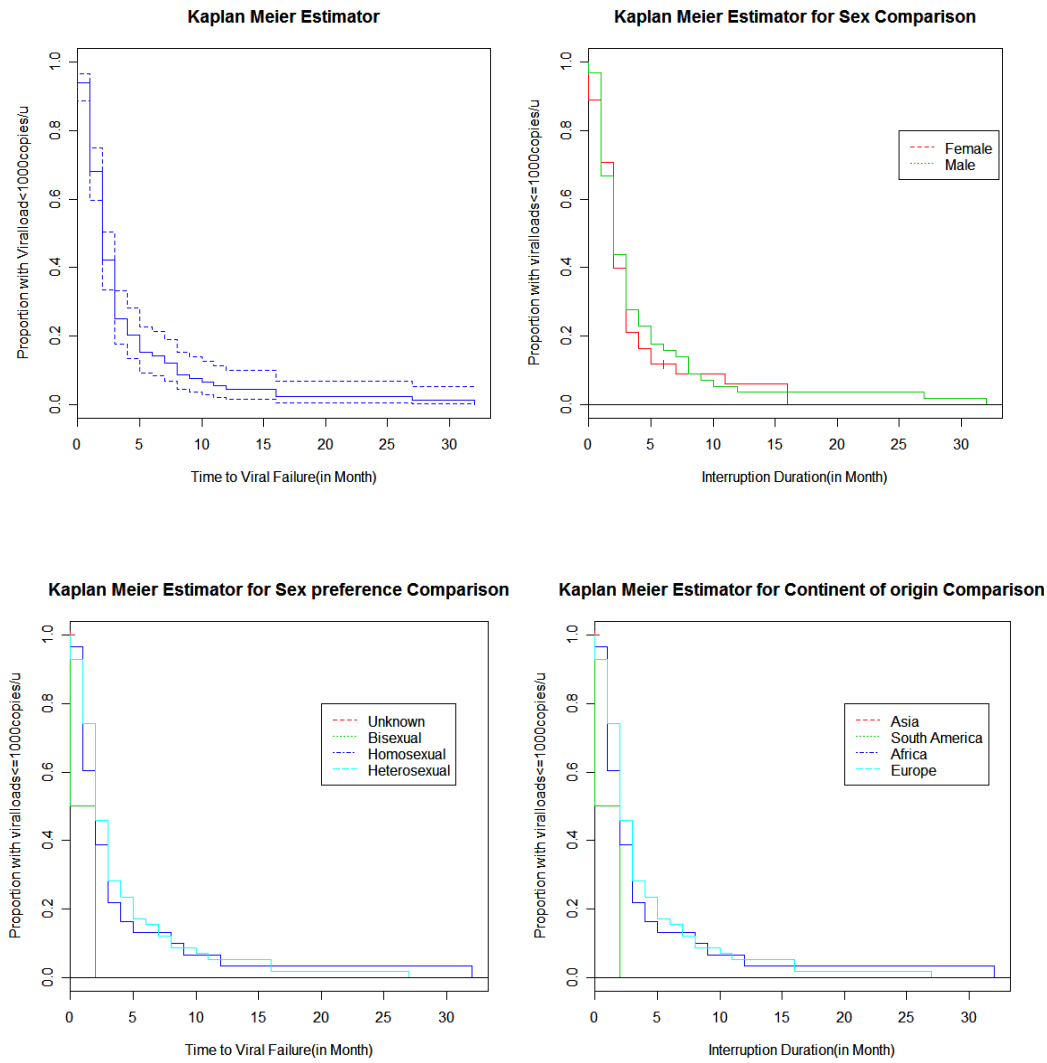


Figure 4: Kaplan Meier survivor estimates for categorical variables (i.e. sex, sex preference and continent of origin)

4.3 Semi-Parametric Cox – Proportional Hazard Model

4.3.1 Univariate Analysis

To start with, univariate analysis is first used in assessing the relationship between failure time and some covariates of interest that are defined in Section 2.1. In handling ties in the covariates, Efron's method is adopted in case there may be many tied failure time. All significant variables at univariate level are included in Multivariate survival model. Table 5 below shows the results of the univariate analysis with *-2loglikelihood, AIC* and *p-value* resulted from the analysis. When all the covariates were used as they were in the dataset, all of them are insignificant at 10% level. Some of them are log transformed and modeled which yields some significant outcome in association with failure time. Variables that are log transformed are the highest viral load before HAART (***vlHAART)***, duration of the disease (***ldisdur***), and duration of viral failure (***lfail***). The detail results

are presented in Table 5 and it is observed that only logarithm transformation of highest viral load before starting HAART, and logarithm transformation of duration of HIV+ infection are significant at 5% level.

Table 5: Univariate analysis of viral load data for chronic HIV-1 patients who interrupt their highly active antiretroviral treatments at ITM, Antwerp, Belgium

Variable	*d.f.*	*AIC*	*-2loglikelihood*	*p-value*
Sex	1	466.051	464.051	0.5530
Age	1	466.320	464.320	0.7730
log (highest Viral load bef. HAART)	1	454.495	452.495	**0.0026**
CD4 HAART	1	373.428	371.428	**0.1980**
Sex preference	1	465.988	463.988	0.5170
Log(disease duration)	1	460.769	456.769	**0.0185**
Log(follow-up duration)	1	466.400	464.400	0.9512
Duration of interruption	1	465.258	463.258	0.2978
Continent of origin	1	466.264	464.264	0.7080

4.3.2 Multivariable Model

In selecting variables for the Cox-proportional model, different methods of model selection are employed. Automatic selection methods like forward, backward and stepwise selection methods are explored and they all yield the same covariates to be finally included in the model. When Collet's method is equally used, we come up with those variables that were obtained using automatic selection procedure. Interaction terms considered show no significant effects and were removed from the model. The final model is presented in Table 6 with significant covariates at 5% level.

Table 6: Parameter estimates (standard error), hazard ratio and 95% confidence interval of Cox-proportional hazards model for chronic HIV-1 patients who interrupt their highly active antiretroviral treatments at ITM, Antwerp Belgium (Viral Load data)

Variable	*Estimate (s.e.)*	*p-value*	*Haz. Ratio*	*95% CIs for HR*
log(disease duration)	1.156 (0.206)	<.0001	3.175	[2.120, 4.756]
log(viral lab value)	0.196 (0.049)	<.0001	1.217	[1.106, 1.339]
CD4HAART	-1.535 (0.742)	0.0386	0.215	[0.050, 0.922]
Interruption duration	-0.063 (0.014)	<.0001	0.939	[0.914, 0.965]

4.3.3 Model Diagnostics

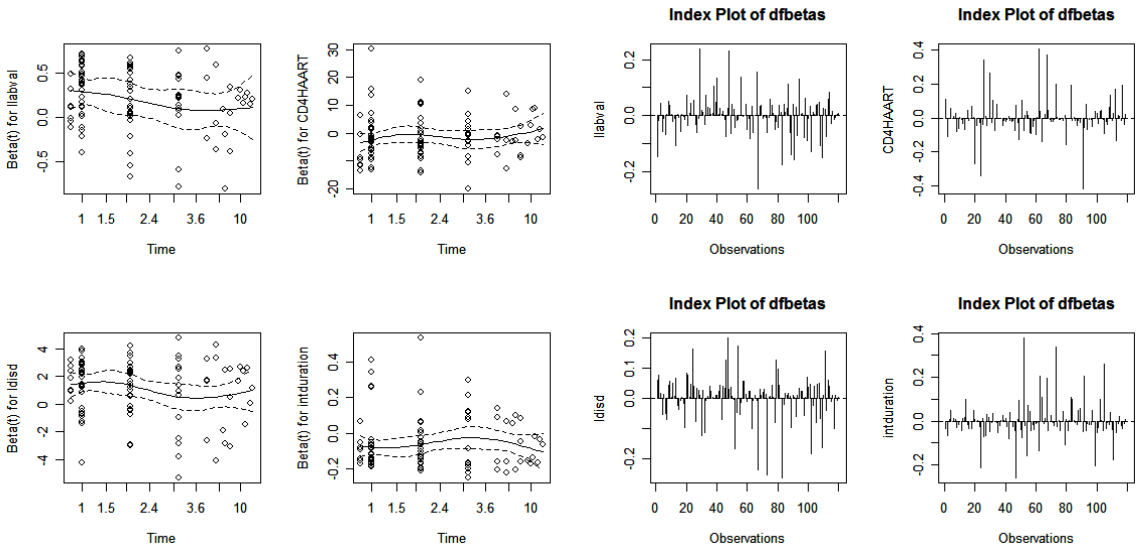
As in the case for a linear or generalized linear model, it is desirable to determine whether a fitted Cox regression model adequately describes the data. In this study, four kinds of diagnostics: for violation of the assumption of proportional hazards; for goodness-of-fit; for outlying (or influential) observations; and for nonlinearity in the relationship between the log hazard and the covariates shall be considered in the following subsections.

(a) Checking Proportional Hazards and Goodness-of-fit

In assessing the adequacy of the fitted model, the assumption of proportional hazards for each covariate in the model is checked. This is done by calculate tests of the proportional-hazards assumption for each covariates using *cox-zph* method implemented in *R* software. A significant result of this test at 5% level indicates violation of this assumption by the covariate. From Table 1 in the Appendix, it shows that assumption of proportional hazards is met by all the covariates and the global test (on 4 degrees of freedom) is statistically nonsignificant indicating that there is general validity of the proportional hazards assumption. Scaled Schoenfeld residuals plot against *log(time)* can also be used to check for proportional hazards assumption. Systematic departures from a horizontal line are indicative of non-proportional hazards. There is confirmation of non-violation of the assumption from the plot (Figure 5(a)) with smoothing line approximately zero. Goodness-of-fit test also estimate R^2 to be 0.35 implying that the model is able to describe 35% variability in the data which is biologically plausible, hence confirming acceptability of the model.

(b) Identification of Influential and Poorly Fit Subjects

Furthermore, a thorough evaluation of regression diagnostic statistic to identify, if any, subjects: have undue influence on the estimates of the Cox regression parameters, or have an unusual configuration of the covariates, or have an undue influence on the fit of the model is carried out using *score residuals*. Leverages, similar to what is obtained in logistic regression, are also adapted into proportional hazards regression through the score residuals as defined by Hosmer (Jnr) and Lemeshow (1998), to examine if there are subjects with undue influence on the fit. This is done through the index plot shown on Figure 5 (b). This plot compares the magnitudes of the largest *dfbeta* values to the regression coefficients and suggests that none of the observations is terribly influential in the study. From the plot we observed that some patients have a large spike and these patients are suspected to have undue influence on the parameter estimates. They are therefore removed one at a time and model refitted without any large change in the model, hence these patients are not influential outliers and then retained in the final model.



(a) *(b)*

Figure 5: Plots of scaled Schoenfeld residuals against transformed log time for each covariate in the model fitted to the viral load data. The solid line is a smoothing-spline fit to the plot, with the broken lines representing a ± 2- standard-error band around the fit (a). Dfbetas plotted against patients' ID to identify patients with undue influence (b)

(c) Nonlinearity Assessment

Nonlinearity, that is, an incorrectly specified functional form in the parametric part of the model, is a potential problem in Cox regression as it is in linear and generalized linear models (Fox 2002). The Martingale residuals are plotted against covariates to detect nonlinearity. From Figure 3 in the Appendix, we observed that log transformation of *viral load at starting HAART* and highest *CD4HAART* do not deviate much from linearity but there is high deviation from linearity on the part of duration of treatments interruption (***intdur***) and log transformation of disease duration variables (***ldisd***). In this case, it may be appropriate to log transform the interruption duration to correct for its nonlinearity.

4.3.4 Model Interpretation

We found four main effects that are statistically significantly associated with the hazard of having viral load higher than 1000 copies/ul. The four main effects are *log transformation of the highest viral load before starting HAART* ***(log(viral lab val))***, *CD4HAART at starting HAART* ***(CD4HAART)***, *log transformation of disease duration* ***(log(disd))*** and *duration of interruption* ***(intduration)***. The CD4 at starting HAART decreases the hazards of experiencing viral failure by a factor $e^{-1.535} = 0.215$- that is, by 78 percent when adjusting for other effects in the model for patient with a unit increase in CD4 at starting HAART. Similarly, the duration of interruption has a

negative effect on hazard of having viral failure by a factor $e^{-0.063} = 0.939$ – that is, decreases the hazard of having viral failure by 6 percent when adjusting for other effects for a patient with a unit increase in duration of treatments interruption. Also, the viral load value at the start of interruption increases the hazards of having viral failure by a factor $e^{0.196} = 1.217$, that is, by 22 percent for a patient with a unit increase in viral load value at starting HAART adjusting for other covariates and finally, duration of disease on log transformation scale increases the hazards of having viral failure when adjusting for other effects by a factor $e^{1.156} = 3.175$ – that is, by more than 100 percent for a patient with a unit increase in disease duration.

The Cox-proportional hazards model is given by:

$$log\left\{\frac{h_i(t)}{h_0(t)}\right\} = 1.156 \times ldisd + 0.196 \times llabval - 1.535 \times cd4haart - 0.063 \times intdur$$

4.4 Interval – Censored Data Analysis

Analysis of interval-censored survival data was carried out by making use of the interval in which the patients' treatments are interrupted since we do not know when exactly the viral rebound occurs. According to Hosmer (jnr) and Lemeshow (1998) and Collet (1994), it is the most frequently encountered type of survival data in practice and also categorized as one of many sources of incomplete observation of survival times that can involve left and right censoring as well as truncation. In order to be able to analyze this type of survival data, the interval given in the data are being made use with the event of interest. That is, the exact failure time is unknown but the interval for each patient is being used. In fitting interval-censored survival, parametric approach, using R-software with ***survreg(Surv(time=begin, time2=end, event, type = "interval"))***, is used with the failure times as intervals. The results of univariate analysis presented in Table 3 in the appendix were used to select variables for multivariate analysis using Collet's method (Collet 1994). Parametric proportional hazard models are fitted into the data, using likelihood ratio test to choose the best one among several models fitted. Table 4 (Appendix) shows the models fitted with their respective *-2loglikelihood* and corresponding p-values. When Weibull model is fitted into the dataset, it reduces the log likelihood drastically, hence this model is preferred to the Exponential model based on likelihood ratio test. Other models compared with Weibull model shows no improvement over the log likelihood and final model is based on Weibull model. The parameter estimates (standard error) are given in Table 7.

Table 7: Estimated coefficients (standard error), Hazard ratio, 95% confidence intervals and p-value for Interval-censored survival analysis of chronic HIV-1 patient with treatment interruption from ITM, Antwerp Belgium (Viral load data) using Weibull parametric regression model

Variable	Estimate (s.e.)	Hazard Ratio	95% CIs for Hazard Ratio	P - value
log(vlab value)	-0.011(0.0016)	1.011	[1.0079, 1.0142]	< 0.0001
log(dis.duration)	0.012 (0.0042)	0.988	[0.978; 0.996]	0.0035
Interruptionduration	-0.0018 (0.0003)	1.002	[1.001; 1.003]	< 0.0001
Log(scale)	-3.236 (0.0675)			< 0.0001
- log λ	6.396 (0.0173)			< 0.0001

4.4.1 Diagnostics of Interval-Censored Survival Data

The same methods used in assessing model adequacy for semi-parametric Cox proportional hazard regression are also employed for Weibull parametric proportional hazard regression in this study. Though for interval-censored data, these diagnostics are not straight forward as we have in Cox model due to interval failure time that is assumed. However, some residuals plots like dfbetas and deviance are used and visual impressions are used in assessing the adequacy of the model and proper remedial measures are taken where necessary.

To start with, we check for model adequacy which is carried out using goodness-of-fit test by given R^2 equals 0.53 indicating that the model is able to explain 53% variability in the data. This implies that the model biologically describes the data well.

Further, assessment of patients with undue influence on the model is done with the help of *dfbetas*, the deviations of individual's effect on the coefficients are plotted against their index number and presented in Figure 6 (a). It is noted that patients with ID numbers 65982, 279972, 357200, are having a large spike with respect to highest viral load before starting HAART, disease duration on log transformaton scale and duration of interruption. These patients are removed one at a time and model refitted without a considerable change in the parameter estimates.

For linearity, we plotted deviance residual which is assumed to approximate martingale residual as we have in Cox proportional model, with lowess smooth. We observed that linearity assumption is violated by highest viral load before starting HAART on log transformation scale, however, the other two variables seem to satisfy the linearity assumption since the lowess smooth is approximate zero line.

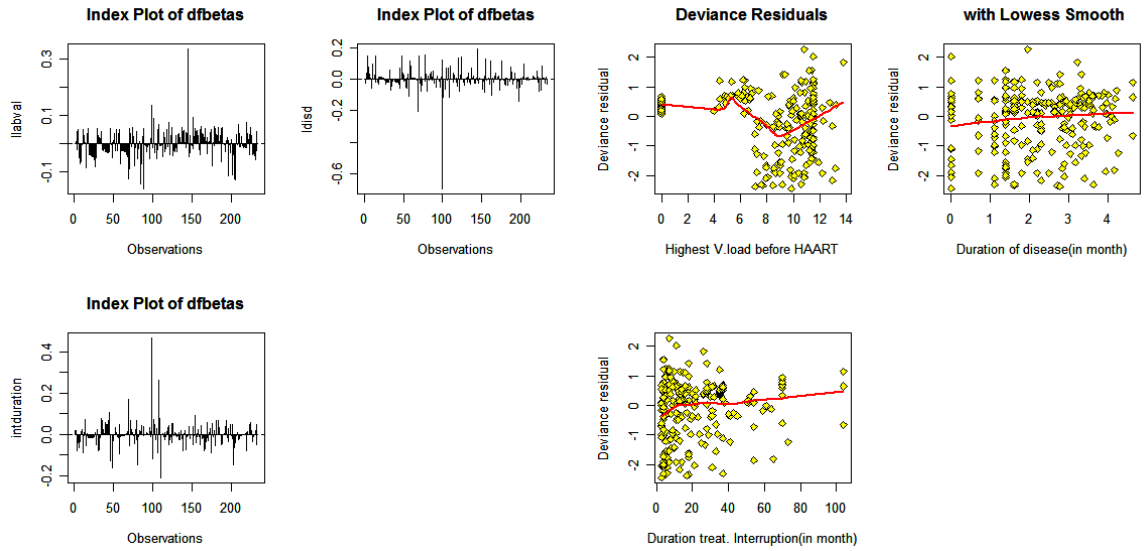


Figure 6: Index plot (a) for dfbetas to identify influential patients and deviance residuals with lowess smooth from local regression to assess linearity on the covariates for Viral load data for chronic HIV-1 patients who interrupt their active antiretroviral treatment at ITM, Antwerp, Belgium

4.4.2 Model Interpretation

From the model, we found that there are three predictors that are significantly associated with the failure time. They are highest viral load before starting HAART on log transformation scale, this variable increases the monthly hazard of having viral failure by a factor (exp - (-0.011) = 1.011) – that is, by 1 percent adjusting for other covariates. This means that the hazard of having viral load failure for a patient that has a unit increase in *viral load at starting* HAART with equal level of other covariates is increase by 1 percent. Similarly, the duration of interruption is found to have small positive impact on failure time. That is, this duration have increase in hazard of viral failure for a patient with a unit increase in the duration of interruption compare to other patients at the same level of other covariates. The duration of viral failures on log transformation scale decreases the hazard of viral failure by a factor (exp -(0.012)) = 0.988, that is by 2 percent. This implies that the hazard of viral load failure for a patient with a unit increase in duration of experiencing the failure is reduced by 2 percent when adjusting for other covariates.

4.5 Analyses of CD4 Data for Patients with Treatments Interruption

4.5.1 Survival Analysis of CD4 Data

Analysis of CD4 is carried out in this section to examine those patients who have their treatments interrupted not as a result of treatment failures. The analyses are done using Kaplan-Meier survivorship estimator, Log-rank test of comparison in categorical variables, Cox proportional

hazard regression model for right-censored data and Weibull proportional regression model for interval-censored data analysis.

4.5.2 Kaplan-Meier for Comparison of Sex, Sex Preferences and Continent of Origin

The Kaplan-Meier *survival* estimator is used in assessing the failure time of patients with respect to CD4 counts. It is observed that the median failure time for CD4 patients who had their highly active antiretroviral treatments interrupted is 3 months, with 95% confidence intervals of 3 – 5 months, which is the same with that of viral load data. The curve is presented in Figure 7 (left panel). From the curve, it shows that there are more events at the beginning of interruption than witnessed towards the end of interruption.

In order to investigate if there is any difference between the failure time for male and female, separate Kaplan-Meier curve are plotted for each sex and this is given in Figure 7 (right panel). From the plot (right hand panel, Figure 7), it seems as if there is no clear difference between the failure time for male and female patients. The median failure time for female is estimated to be 3 months with 95% confidence interval of 2 – 7 months. Male has a median failure of 3 months with 95% confidence interval of 2 – 5 months indicating that median failure time for female and male are the same but female has wider interval than male.

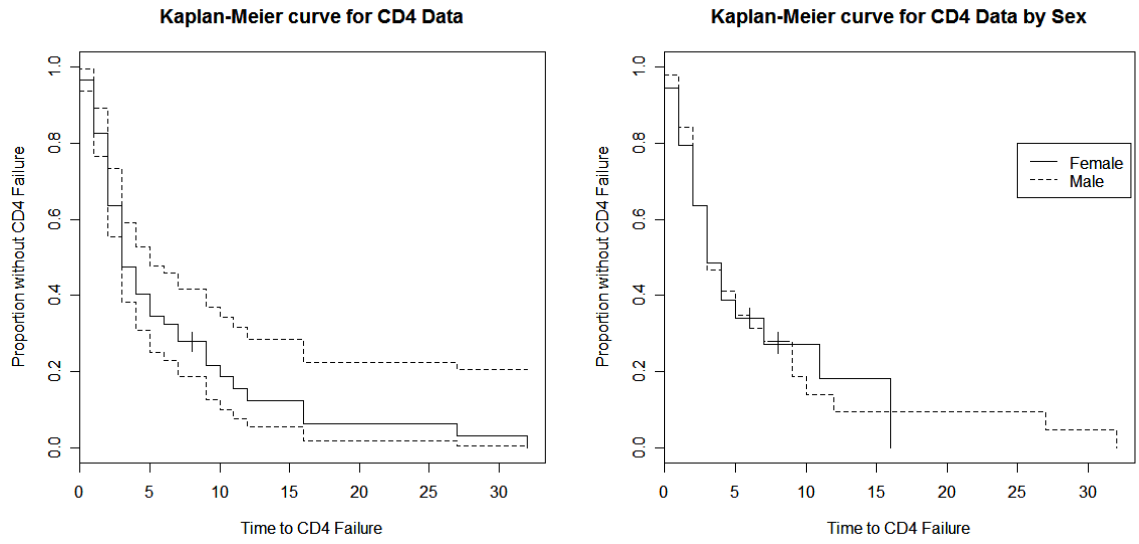


Figure 7: Kaplan-Meier survivor estimates for overall and for sex comparison using CD4 data of chronic HIV-1 patients who interrupt their highly activey antiretroviral treatments at ITM, Antwerp, Belgium

The survivorship estimate curve for sex preference (Figure 5, in the appendix) shows that there seems not to be difference in the failure times for homosexual and heterosexual patients since these curves overlap each other. The median failure time for homosexual patients is found to be 3

months (95% CIs 3 – 5 months) while that of heterosexual patients is estimated to be 3 months (95% CIs, 3 – 6). Comparing the *continent of origin* using Kaplan-Meier survivorship estimates shows that patients from Europe experience higher survival time than patients from African (Figure 5 appendix). The median failure time for Africa and Europe patients are respectively 3 months (95% CIs, 3 – 6 months) and 3 months (95% CIs, 3 – 5 months). The next section is devoted to Log-rank test to ascertain what is noted from Kaplan-Meier survivorship function using non-parametric approach.

4.5.3 Log-Rank Non-parametric test of comparison of survivorship estimates

A non-parametric test for the null hypothesis of equal median survivorship is carried out using log-rank test. We first conducted a test for equality of failure time between male and female. The test shows that there is no significant difference in failure time between male and female patients (p-value = 0.814). Similarly, it is found that statistically, there is no significant difference in failure time of homosexual patients and heterosexual patients (p-value = 0.771). For the continent of origin, similar result is obtained indicating that the failure times for patients from different continents, most especially between Africa and Europe patients, are not significantly different at 5% level (p-value = 0.593).

4.5.4 Cox-Proportional Hazards Regression Model for CD4 Data

Since log-rank test is a non-parametric procedure of testing significant difference between two or more prognostic factors in survival data, this test has a set-back that it cannot accommodate other covariates of interest. Therefore, it serves as marginal (or univariate) approach to testing significant difference between two or more prognostic factor. Cox-proportional regression is a semi-parametric way of assessing the contribution of each prognostic factor to failure time in the presence of other covariates.

After using different methods of model selection, we finally come up with the following covariates as risk factors explaining time CD4 failure; *percent change in CD4; duration of drug holiday and duration of disease on log transformation scale*. The final model is given in Table 8. Therefore, the Cox-proportional hazards model is given by;

$$log\left\{\frac{h_i(t)}{h_0(t)}\right\} = 1.588 * ldisd - 0.122 * intduration - 0.042 * pctchange$$

Where $h_0(t)$ is the baseline hazards

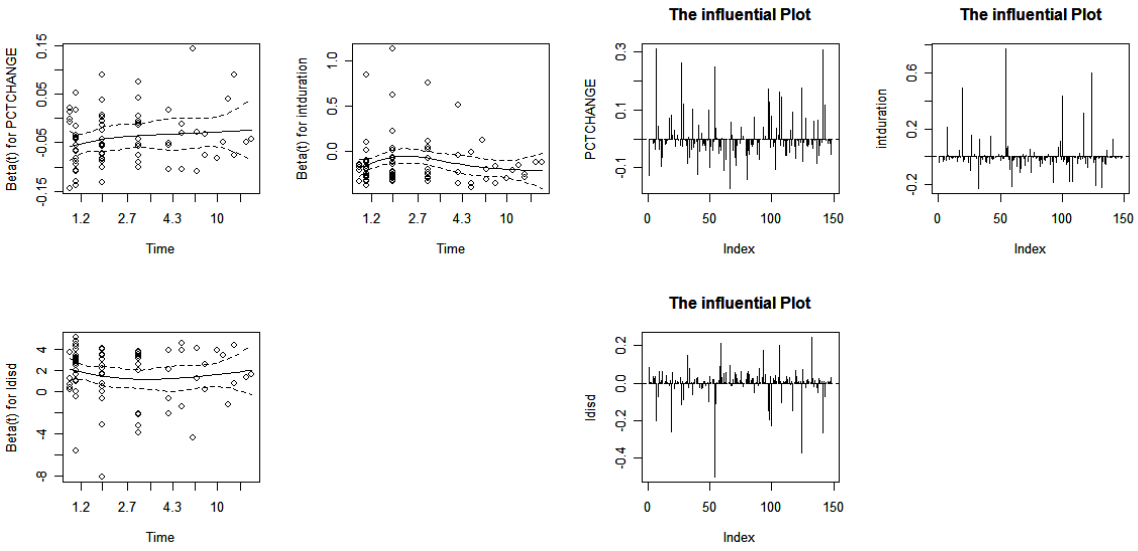
Table 8: Estimated coefficients (standard error), Hazard ratio, 95% confidence intervals for Hazard ratio and p-value for Interval-censored survival analysis of chronic HIV-1 patient with treatment interruption from ITM, Antwerp Belgium (CD4 load data) using Cox proportional Hazards model

Variables	Estimate (s.e.)	Hazard Ratio	P - value	95% CIs for Hazard ratio
Percent Change	-0.042 (0.00712)	0.959	< .0001	[0.946 , 0.972]
Interrupt duration	-0.122 (0.02178)	0.885	< .0001	[0.848, 0.924]
log(disea. duration)	1.588 (0.257)	4.892	< .0001	[2.956, 8.096]

4.5.5 Assessment of Cox Proportional Hazards Model Adequacy

Checking for Proportional hazards Assumption: In assessing the validity of proportional hazards assumption, cox-zph is used and the test shows that the assumption is valid for all the variables, p-value for each variable is not significant at 5% level and GLOBAL test also validates general acceptability of the proportional hazard assumption (p-value = 0.411). These variables are plotted with scaled Schoenfeld residuals against transformed failure time and overplayed with lowess smooth to graphically investigate the proportional hazard assumption. From Figure 8 (a), we observed that there is no departure from horizontal line in the lowess smooth validating the proportional hazard assumption. In addition, time-dependent covariates model which consists of interaction between *log failure time* and those variables in the model, but the interactions are not significant at 5% level indicating the validity of proportional hazard assumption (Table 4 in the appendix).

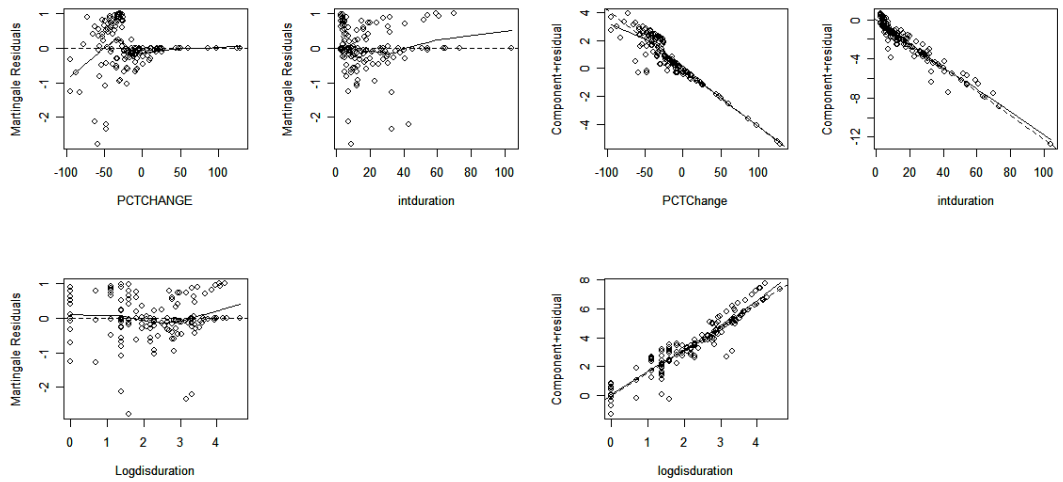
Checking for Influential Observations: Index plot of *dfbetas* against the patients' index numer for CD4 data is used to identify individuals that may highly influence the study. From the plot in Figure 8 (b), we observe that there are some patients with large spike (e.g. patients with ID = 10783, 411049 and 244581 with respect to percentage change in CD4 counts) in the plot indicating that these individuals may have undue influence in the analysis. The remedial measure taken by removing these patients one at a time and regression model refitted shows no considerable change in the parameter estimates. These patients are considered not to be influential and included in the final model.



(a) *(b)*

Figure 8: Plots of scaled Schoenfeld residuals against transformed time (a) and dfbetas plot to identify influential patients (b) for each covariate in Weibull model fit to chronic HIV-1 patients who interrupt their active antiretroviral treatment at ITM, Antwerp Belgium

Checking for Linearity Assumption: In order to assess the linearity assumption on the part of the covariates, we plot Martingale residuals against each of the covariate and overplayed with lowess smooth produced from local linear regression and we found that there are signs of nonlinearity in the three continuous covariates (Figure 9(b)) indicating that the assumption of linearity is slightly unsatisfied. Therefore, transformation of these variables may be recommended to linearise them or stratify them to change them to categories (Fox 2002).



(a) *(b)*

Figure 9: Martingale residuals (a) and component-plus-residual plots (b) for the covariates Pctchange, intduration, and disease duration on log transform scale. The broken lines on the residual plots (b) are at the vertical value 0, and on the component-plus-residuals plot are fit by linear least-squares; the solid lines are fit by local regression (lowess)

4.5.6 Model Interpretation

The hazards of having CD4 below 20% for a patient with a unit increase in percentage change in CD4 count is less by 4% when adjusting for other covariates in the model. In addition, for a patient with a unit increase in drug holiday, the hazard of CD4 failure is reduced by 12% whereas for a patient with a unit increase in duration of disease on log transformation scale, the hazard of CD4 failure is increased in multiple folds, that is more than 100% times.

4.6 Interval-Censored Survival Analysis of CD4 Data

The interval-censored survival data fitted into the data using *survreg* procedure in R with two time points, *stophaart* and *failtime* which are times when patients resume drug holiday and when he/she tested to CD4 below 20% respectively. The result of univariate analysis is presented in Table 4 in the Appendix. After univariate analysis, all variables that are significant at 20% level are included in multivariate analysis and Collet's method of model selection is followed to select the variables for potential final model. The variables that are significant at the final selection are presented in Table 9.

Table 9: Parameter Estimates, hazards ratio, 95% confidence interval and p-value for interval-censored survival data for CD4 data of chronic HIV-1 patients who interrupt their active antiretroviral treatment at ITM, Antwerp, Belgium

Variable	Estimate (s.e.)	Haz Ratio	95%CIs for Haz Ratio	p-value
CD4 LABVAL	0.033 (0.0145)	0.968	[0.94, 0.995]	0.0219
PCT CHANGE	0.0013 (0.000167)	0.999	[0.998, 1.000]	< 0.0001
Inter. duration	-0.0014 (0.000204)	1.001	[1.000, 1.0014]	< 0.0001
Trt. duration	0.00024 (0.0000917)	1.000	[.999, 1.0005]	0.0094
South America	0.0856 (0.0492)	0.918	[0.834, 1.011]	0.0818
Africa	0.0812 (0.0353)	0.922	[0.860, 0.988]	0.0214
Europe	0.0648 (0.0352)	0.937	[0.875, 1.004]	0.0653
Log(scale) log(λ)	-3.369 (0.0691)			< 0.0001
-log(γ)	6.267 (0.0357)			< 0.0001

4.6.1 Model Diagnostics

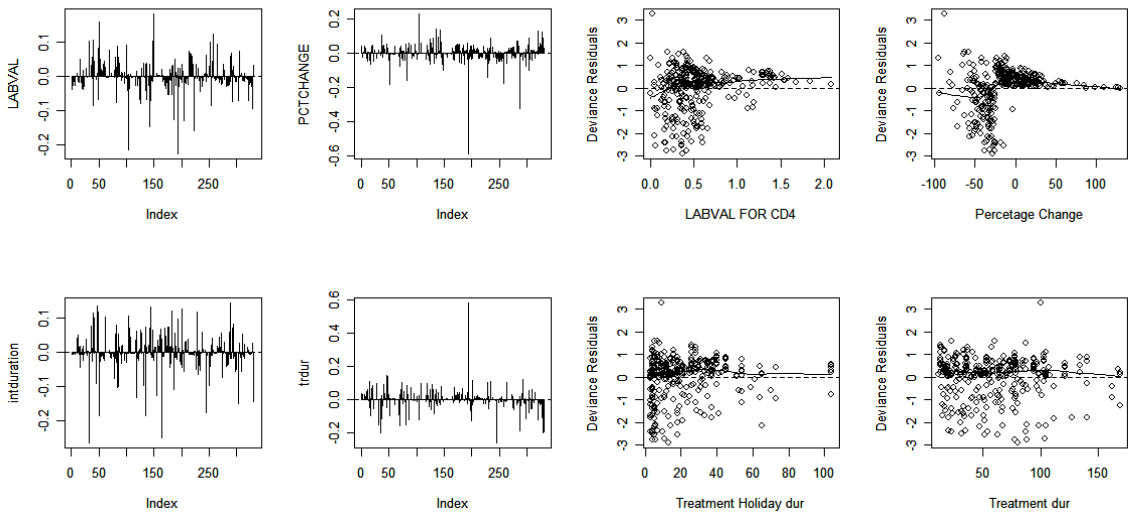
Assessment of model adequacy in interval-censored data in survival analysis is not straight forward as we have in right-censored survival analysis. In the first instance, model adequacy in terms of goodness-of-fit is examined using R^2 that is analogous to linear regression analysis

measure of goodness-of-fit that was proposed by Cox and Snell (1989) to assess goodness-of-fit for the Cox proportional hazard model. This is given to be

$$R^2 = 1 - exp\left[\frac{2}{N}\left(LL_0 - LL_{\hat{\beta}}\right)\right]$$

Where $LL_{\hat{\beta}}$the log likelihood for the Weibull proportional hazard model is, LL_0 is the log likelihood for model without any covariate and *N* is the number of time interval in the event sequence. Therefore, for this model, the final R^2 is 0.437, thus the Weibull model seems to describe the data well (Li et al. 2006).

In assessing if there are any outlying patients, we use *dfbetas* residuals as proposed by Hosmer (Jnr) and Lemeshow (1998), from Figure 10 (a), we found that some patients are having large deviance with respect to all the continuous covariates. This brings suspicion on these patients, they are deleted one at a time and Weibull parametric regression refitted without any significant noticeable change in the model, and hence these patients are considered not to be outliers and included in the model. Also we check for linearity of the continuous covariates using deviance residuals with lowess smooth being overlaid. From Figure 10 (b), it was observed that nonlinearity is not apparent since the lowess smooth has not deviated much from zero in all covariates.



(a) *(b)*

Figure 10: Index plot of dfbetas (a) for each patient to identify influential subjects in the analysis and deviance residual plot(b) to assess the linearity of the covariates in Weibull proportional hazards model for chronic HIV-1 patients who interrupt their highly active antiretroviral treatments at ITM, Antwerp, Belgium

4.6.2 Model Interpretation

The final model is therefore given as we have in Table 9. From the model, we observed that the hazard of CD4 failure for a patient with a unit less in highest CD4 before starting HAART is reduce by 3% when adjusting for other covariates. Also the hazard of CD4 failure is almost the same with that of patient with a unit increase in percentage change in CD4 counts when adjusting for other covariates in the model. However, for a patient with a unit increase in duration of interruption, the hazard of CD4 failure is slightly increase by approximately 1%. In the case of treatment period, there is no difference in hazard of CD4 failure for all the patients at that duration level when adjusting for other covariates. Considering patients from continent of origin perspective, we found that the hazard of CD4 failure is reduced by 8% for a patient from South America to that of patient from Asia, irrespective of the level of other covariates. Similarly, there is also a reduction of 8% and 6% respectively for patients from Africa and Europe compare with patient from Asia who is at the same level of other covariates.

4.7 Assessing the Impact of Missingness in Viral load data Analysis

In the viral load data, we observed some missingness in one of the covariates that are significantly associated with failure time. In order to assess the impact of missingness on the parameter estimates, multiple imputation technique with 5 imputations is used in imputing for the missing values in the variable *CD4HAART* and Cox-regression model refitted and the result compared. Table 10 consists of Cox-proportional regression parameters with missing values and with imputation. The parameter estimates are found to be different indicating that the missingness has impact on the estimates. The impact shows that analysis with missingness over-estimates the hazard ratio meaning that the parameter estimates are equally over-estimated. Since none of the variables selected for interval-censored analysis are with missingness, the assessment is not necessary in that regard.

Table 10: Comparison of Cox proportional regression model with missingness (N = 120) and without missingness (N = 148) for viral load data analysis of chronic HIV-1 patients who interrupt their treatments at ITM, Antwerp, Belgium

Variable	**Est. (s.e.) (with missing)**	**Hazard Ratio**	**p-value**	**Multiple imputation**	**Hazard Ratio**	**p-value**
log(dis. duration)	1.155(0.206)	3.175	<.0001	0.903 (0.185)	2.467	<.0001
log(viral labval)	0.196 (0.049)	1.217	<.0001	0.164 (0.043)	1.178	0.0001
CD4HAART	-1.535 (0.742)	0.215	**0.0386**	-0.595 (0.868)	1.813	**0.5042**
Inter. duration	-0.063 (0.014)	0.939	<.0001	-0.057 (0.012)	0.945	<.0001

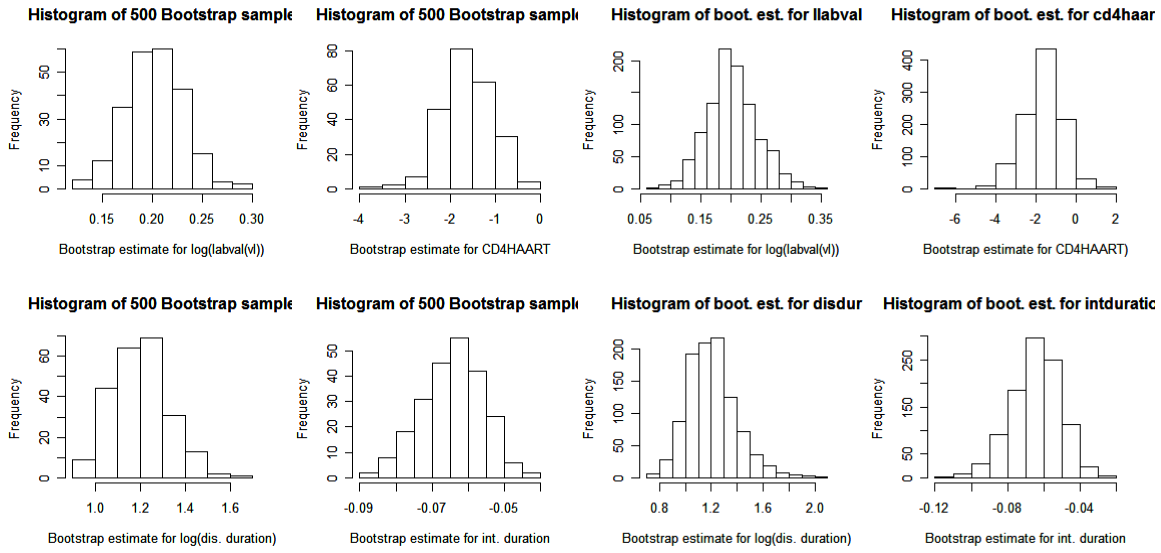
4.7 Model Validations using Non-Parametric Bootstraps

In order to make the model acceptable, it is always of scientific interest to validate it using other dataset or part of the available data. In survival analysis, some papers use bootstrap method proposed by Efron (Efron and Tibshrani 1993) to validate a proposed model, either in a parametric way or non-parametric depending on the model fitted. Since Cox proportional hazard model is 'distribution free', therefore, it is appropriate to use nonparametric bootstrap for its validation but parametric method, being preferred to nonparametric in a case whereby the model assumes a specific distribution, is adopted for Weibull proportional hazards model in this study.

Nonparametric bootstrap for Cox proportional hazards regression model as shown in Table 11 are the estimates obtained from the Cox proportional hazard model and those of 500 and 1000 nonparametric bootstrap estimates for viral load data. From Table 11, we observed that the bootstrap estimates closely approximate those of the real estimates. Figure 11 shows the histograms for the bootstrap estimates for each variable in the model. These graphs show that the bootstrap samples are approximately normal. However, the estimates from the parametric Weibull regression model are not approximate those of the real values and call for more attentions.

Table 11: Bootstrap samples for Cox proportional hazards regression model with bootstrap sample of 500 and 1000 for viral load data

Variable	**Actual Estimate (s.e.)**	**500 Bootstrap Estimate (s.e.)**	**1000 Bootstrap Estimate (s.e.)**
ldisd	1.155 (0.206)	1.220 (0.208)	1.205 (0.191)
llabval	0.196 (0.049)	0.202 (0.043)	0.202 (0.0416)
CD4HAART	-1.535 (0.742)	-1.739 (1.025)	-1.623 (0.968)
intduration	-0.063 (0.014)	-0.065 (0.0148)	-0.065 (0.0137)



(a) *(b)*

Figure 11: Histograms for the 500(a) and 1000(b) bootstrap samples for validation of Cox proportional hazards regression model for viral load data obtained from chronic HIV-1 patients who interrupt their highly active antiretroviral treatment at ITM, Antwerp, Belgium

4.8 Model Comparison

The two major models fitted to the data used in this study worth being compared. It is observed that in the analysis of viral load failure, the risk factors that are significantly associated with the failure time are viral load at start of HAART on log transformation scale, disease duration on log transformation scale, duration of interruption for Weibull regression model and addition of CD4 at start HAART for Cox proportional regression model. The main difference noted from these models is that for most of these variables there hazards ratio are in opposite direction in the two models except for viral load at HAART that has the same effect but smaller in Weibull model than in Cox proportional hazards model. Similar difference is noticed from the analysis of CD4 immunological failure. This difference may result from the fact that Cox proportional hazards model is not following any given distribution and estimates its parameters by maximizing partial log likelihood whereas Weibull model has a full distribution and estimates its parameters by maximizing log likelihood. Another reason for the differences may be due to the fact that the right-censored analysis using Cox regression uses exact time point which is the relative difference between starting date of interruption and fail date whereas the interval-censored analysis uses the two endpoints.

5.0 Discussion and Conclusion

The development and introduction of highly active antiretroviral treatments (HAART) have led to a dramatic drop in mortality among HIV infected patients, at least in those regions in the world where the majority of patients are accessible to HAART. HAART suppresses viral replication and allows the immune system to recover, as measured by increase in CD4 cell counts. It is however, generally accepted that HAART cannot eradicate the infection and as such needs to be taken life-long. The high cost of HAART and the frequent, serious, side effects have led investigators to explore the possibility of interrupting HAART in a controlled manner (structured treatment interruption, STI).

The main objects of this study were to examine the outcome of patients with chronic HIV-1 infection whom their treatments were stopped for reasons other than treatment failure through their rebound of plasma viral load, decrease in CD4 cell count and clinical events. Also it was meant to explore and come up with factors that are predictive of 'good control' of the infection.

The data obtained contain 1296 patients in total with 148 (11%) patients having their viral loads recorded and 133 being record on CD4 percentage. We observed that the mean age of the patients in interruption group and those of non-interruption group are respectively 36 years and 37 years. Statistical test shows that there is no significant difference in the age of the two groups (p-value = 0.1506). In addition there are 876 male patients accounting for 68% of the patients in the study and in general, majority of the patients are from Europe (62%). In terms of sexual preference, there are 715 patients in heterosexual group which is 55% out of 1296 patients showing that majority are heterosexual in nature.

Kaplan-Meier survivorship estimate is used to explore the differences in sex, sexual preference and continent of origin with respect to viral and CD4 failures. From the estimates, we found that median time to viral failure is generally 3 months but for all sex, sexual preference groups and continent of origin, their median failure time is 2 months. Log-rank test performed to examine if there are differences in the risk groups for all the three categorical variables show that there is no significant difference in each of the risk group separately.

Analysis of right-censored data is carried out with Cox regression model where univariate analysis shows that only *VLHAART*, *CD4HAART* and duration of the disease are the risk factors predicting the viral load rebound in the patients. These variables were used in the multivariate analysis with inclusion of other non-significant variables and we finally have four variables that are risk factors that jointly serve as predictive of 'good control' of slow rebound of plasma viral load. These

variables are *disease duration on log transformation scale,* which increases hazard of having viral failure by more than 100% for a patient with a unit less in the duration of the disease. Also we have the viral load at the beginning of interruption having 22% percent increases in hazard of having viral failure. Also is the *CD4HAART* and duration of treatment interruption with reduction of 79% and 9% respectively in hazard of having viral load failure. Interval-censored analysis is fitted using Weibull distribution proportional hazard model since the actual failure time is unknown and we found that all the variables discovered when using Cox regression are equally found associated with viral failure except *CD4HAART*. The influence of these variables on failure time is not difference from what we obtained using right-censored data but in small magnitudes.

From the Kaplan-Meier 'survivorship' estimates conducted for CD4 data, there shows that the median time for all the risk groups (sex, sex preference and continent of origin) are 3 months for each of them. Log-rank test shows that there is no significant difference in each of the risk groups with highly non-significant p-values. These indicate that the risk groups are not predictive of 'good control' with respect to CD4 failure. Cox proportional hazards model reveals that the following variables are predictive of 'good control' on CD4 failure; percentage change in CD4, duration of treatment interruption, duration of treatment, and continent of origin. When these variables are introduced into multivariable model and other non significant variables are tested along with them, we finally found three variables that are significantly associated with the CD4 failure which are percentage change in CD4 with a decrease contribution to hazard of CD4 failure (4%), in addition we found duration of treatment interruption also reduces month hazard of having CD4 failure by 12% and duration of disease on a log transformation scale which increase monthly hazard of CD4 failure by more than 100%.

Weibull proportional hazards regression model, being a parametric proportional model for interval-censored survival analysis at initial univariate stage shows that only three variables are risk factors for CD4 failure which are percentage change in CD4 cell counts, CD4 lab values, and duration of treatment. These variables are multivariably modeled and all of them in addition to interruption duration and continent of origin are found to be significantly associated with CD4 failure. All these variables are found to have a small magnitude decrease in monthly hazards of CD4 failure with average of 8% except interruption duration and treatment duration which have no contribution to monthly hazard of having CD4 failure.

Since *CD4HAART* is a variable associated with viral failure with significant amount of missingness, implication of these missing observations is investigated with multiple imputation technique and we found that there is over-estimation in parameter estimates with missingness

compare to complete data as well as hazards ratios being over-estimated. Model validation carried out using 500 and 1000 nonparametric bootstrap samples show close approximation in the parameter estimation with those obtained at the initial analysis using Cox regression model.

In conclusion, we found in this analysis that patients with treatment interruption experience viral failure as well as CD4 failure at an early stage since interruption. This implies that they experience high rise in viral load rebound and considerable decrease in CD4 counts at an early stage of the interruption which may be detrimental to their living. This means that if they continue on this drug holiday, there may be loss of life on the part of those that stopped their treatments. It is therefore essential for these patients to continue using their treatments as recommended by medical experts in order to continue living a normal life.

6.0 Reference

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7.0 Appendix

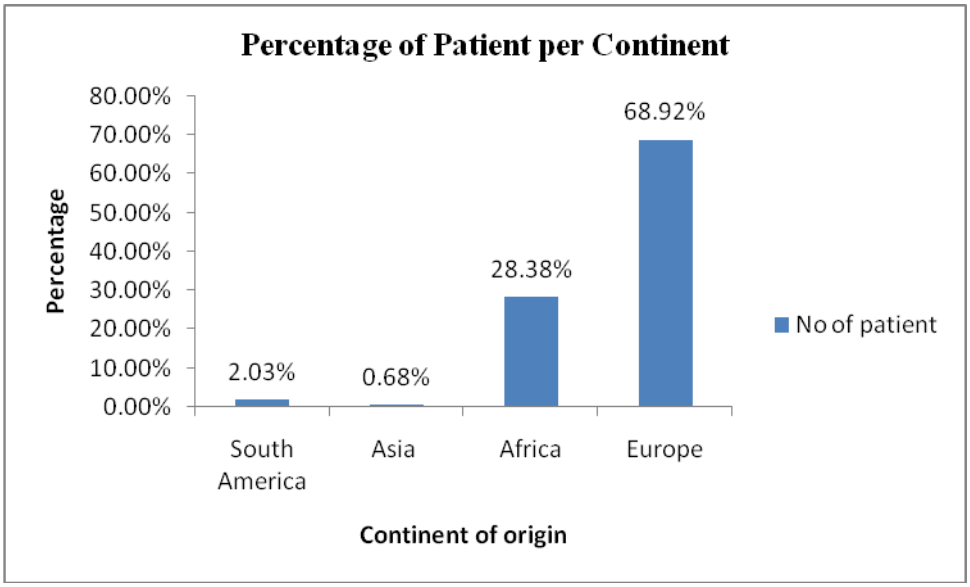


Figure1: Bar-Chart showing the percentage of patients according to continent of origin

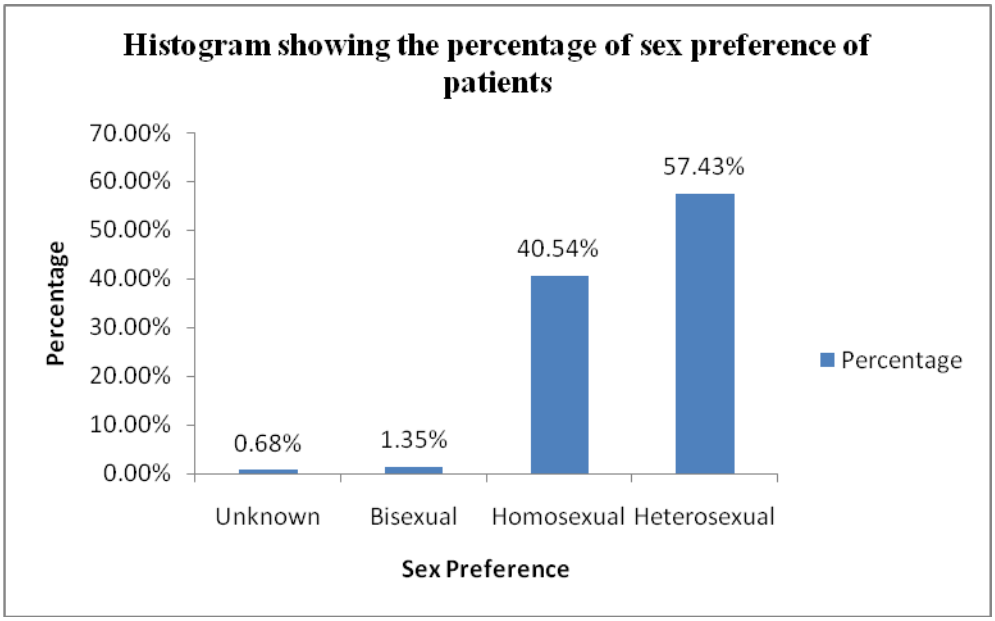


Figure2: Bar-Chart showing the percentage of patients according to sex preference

Table1: Test for Proportional hazard assumption using Cox zph model

	rho	chisq	p-value
llabval	-0.2323	2.825	0.0928
CD4HAART	0.0968	1.085	0.2975
ldisd	-0.1607	2.821	0.0931
intduration	0.0428	0.221	0.6379
GLOBAL	NA	5.648	0.2270

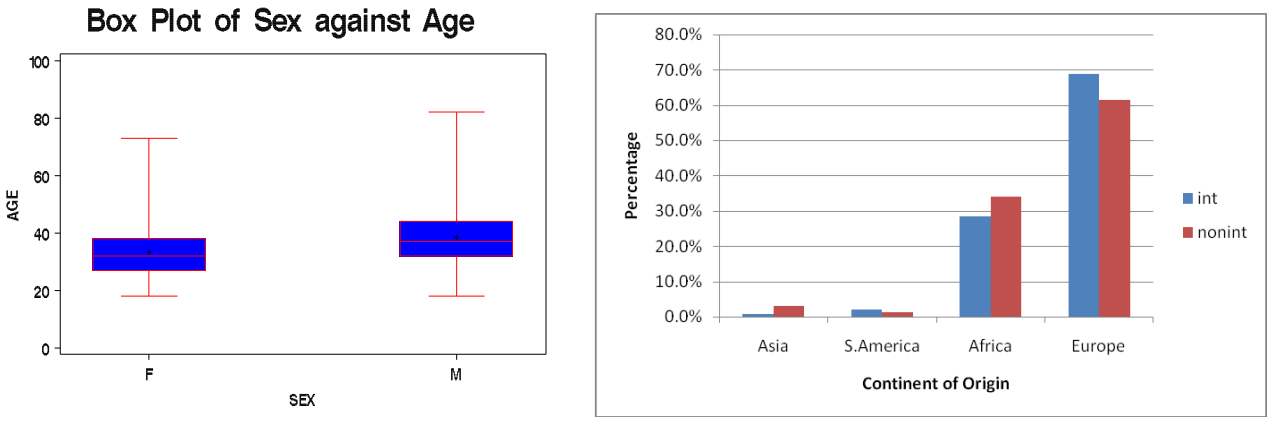


Figure 3: Box plot showing the distribution of age between the male and female patients who interrupt their treatments and Bar-Chart showing the distribution of patients with and without treatment interruption according to Continent of origin at ITM, Antwerp, Belgium

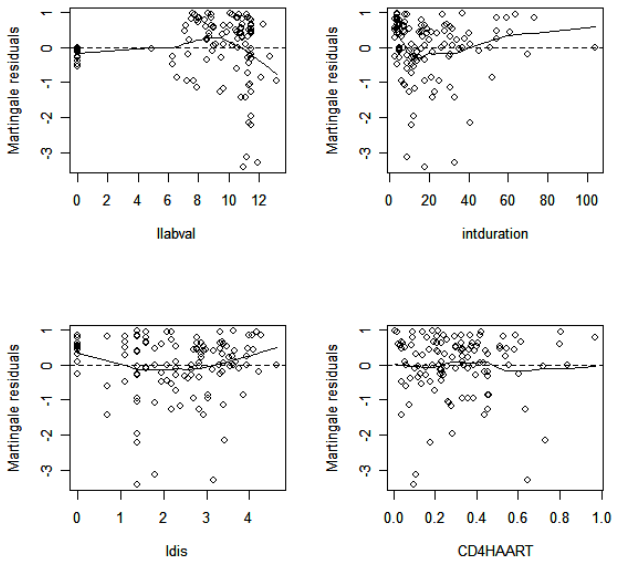


Figure 4: Plot of Martingale residuals against continuous variables to check linearity in viral load data using Cox proportional hazards model

Table 2: Selection of best distribution for the Analysis of Viral load data using interval-censored survival for chronic HIV-1 patients who interrupt their treatments at ITM, Antwerp, Belgium

Model	-2Loglikelihood
Exponential	2226.4
Weibull	**1442.4**
Lognormal	1457.8
Gaussian	1455.8
loglogistic	1462.6
Logistic	1461.4

Table 3: Univariate analysis of Viral load data using interval-censored survival

	Weibull Model	
Variable	loglikelik	p-value
Sex		
Sex pref	-775.2	0.017
CD4HAART	-605	0.904
Age	-777.9	0.00015
Log fail duration	-727.4	0.0252
Log disease duration	-777.2	0.202
log labvalue	-736.2	< **0.0001**
Duration of interruptio	-777.3	**0.0004**
Log follow up duratn	-775.4	0.0151
Treatment duration	-777.4	0.342
Continent of origin	-777.3	0.261

Survival analysis of CD4 Data Analysis

Table 4: Univariate Analysis of CD4 data of chronic HIV-1 patients who interrupt their active antiretroviral treatment at ITM, Antwerp, Belgium

	Cox-Proportional Model			**Weibull Model**	
Variable	AIC	-2loglikelihood	p-value	loglikelik	p-value
Sex	572.508	570.508	0.817	-768.6	0.837
Sex pref	572.485	570.485	0.7836	-768.5	0.655
CD4HAART	407.381	405.381	0.6038	-583.3	0.665
Age	571.878	569.878	0.4187	-768.6	0.799
Log fail duration	550.981	548.981	0.5991	-721.5	0.331
Log disease duration	571.595	569.595	0.3271	-768.6	0.724
CD4 interruption	563.713	561.713	**0.0018**	-768.3	0.43
CD4 nadir	572.251	570.251	0.5749	-768	0.272
percentage Change	559.954	557.954	**0.0007**	-697.3	< **.0001**
CD4labvalue	572.548	570.548	0.9107	-744.2	< **.0001**
Duration of interruptio	568.120	566.120	**0.0502**	-764.8	**0.0021**
Log follow up duratn	572.358	570.358	0.6506	-768.4	0.546
Treatment duration	568.661	566.661	**0.0415**	-764.6	**0.0047**
Continent of origin	571.878	566.661	**0.0415**	-768.5	0.699

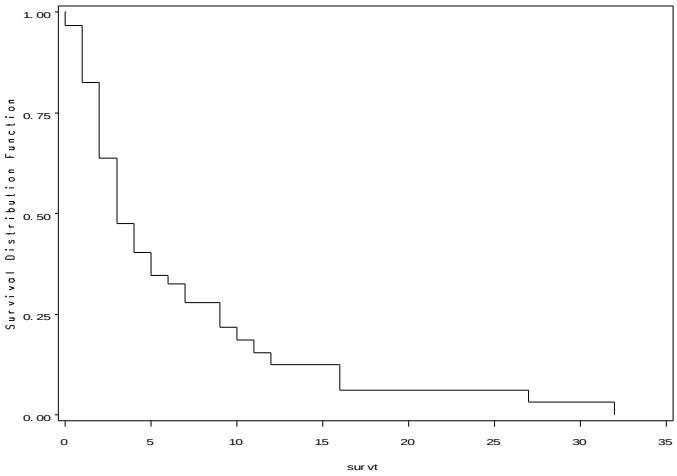


Figure 5: Kaplan-Meier survival estimator of failure time of chronic HIV-1 patients with treatment interruptions at ITM, Antwerp, Belgium

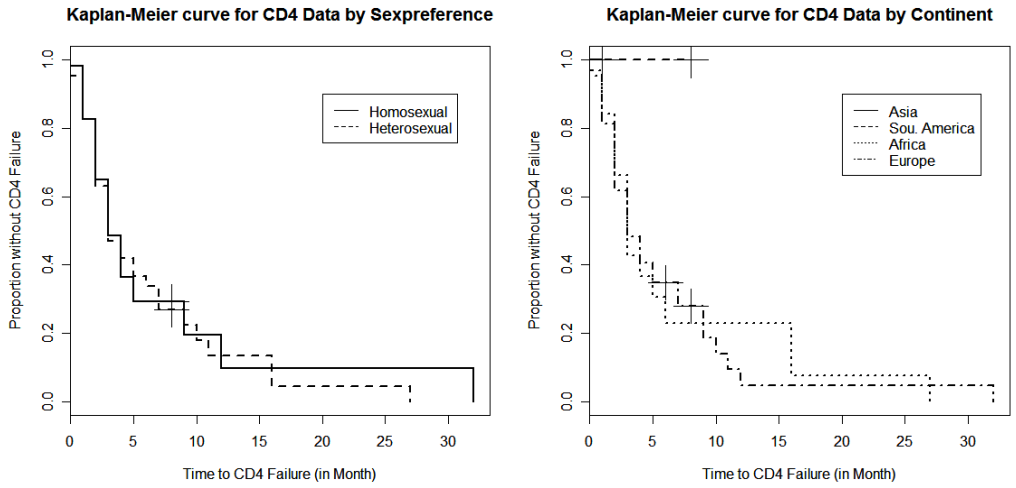


Figure 6: Kaplan-Meier survivorship estimates for sex preference and continent of origin for chronic HIV-1 patients who interrupt their actively antiretroviral treatment at ITM, Antwerp, Belgium

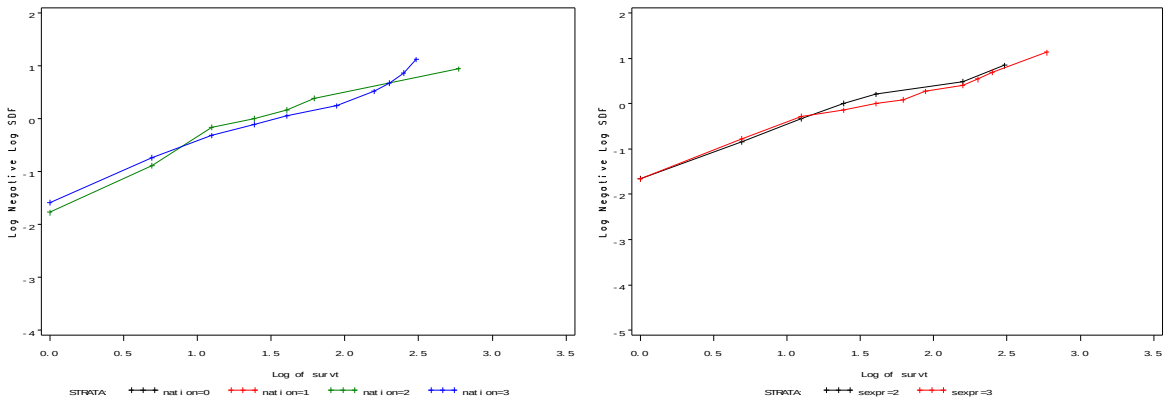


Figure 7: Plot of log(-log(SDF)) versus log of failure time for continent of origin (left panel) and sex preference (right panel) in CD4 data

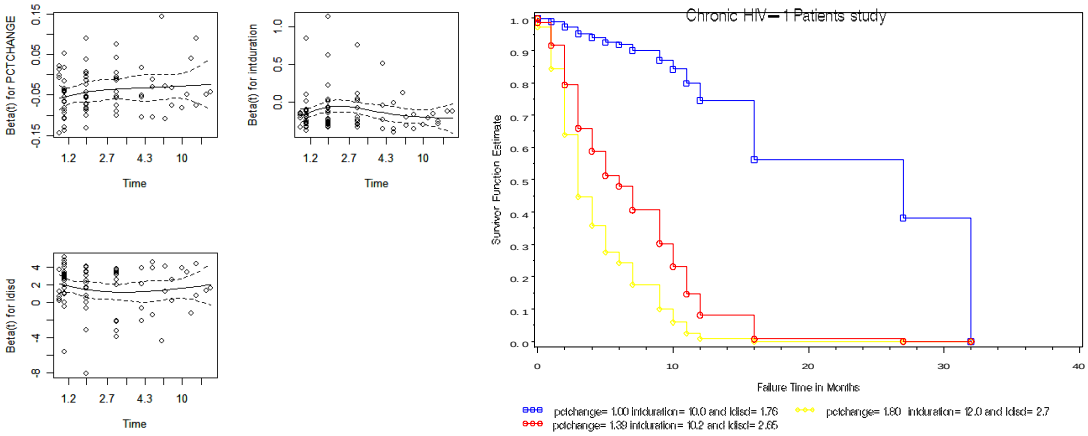
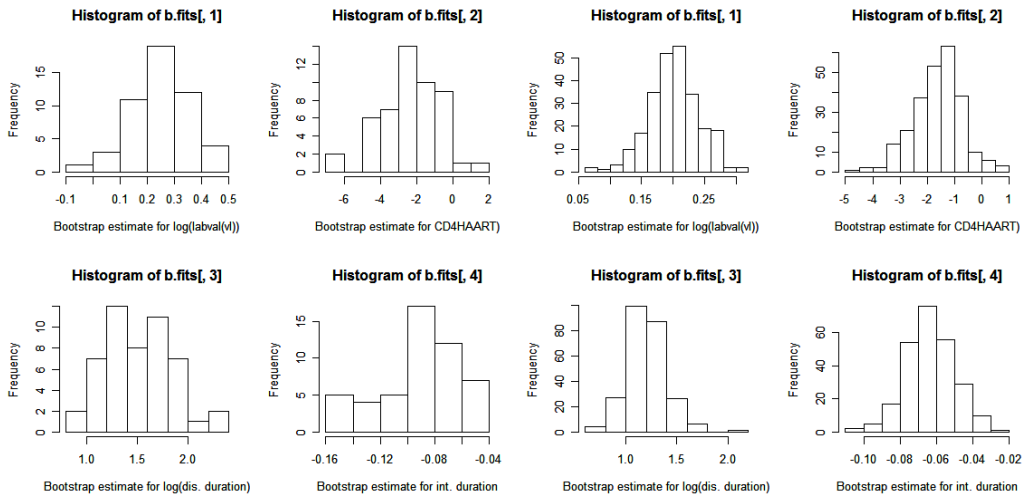


Figure 8: Graphical (Scaled Schoenfeld residuals for each variable against transformed time) test for proportional hazard assumption for CD4 data of chronic HIV-1 patients who interrupt their highly active antiretroviral treatment at ITM, Antwerp, Belgium and estimated survival function for CD4 data

Table 4: Statistica test for proportional hazard assumption for CD4 data of chronic HIV-1 patients who interrupt their highly active antiretroviral treatment at ITM, Antwerp, Belgium

Variable	Estimate (s.e.)	p-value	HR
PCTCHANGE	-0.056 (0.012)	<.0001	0.945
intduration	-0.1001(0.032)	0.0015	0.904
Logdis.durat	1.885 (0.440)	<.0001	6.584
Logt*pctch	0.011(0.010)	**0.2614**	1.011
Logt*intdurat	-0.027 (0.031)	**0.3847**	0.974
Logt*ldisdur	-0.163 (0.351)	**0.6422**	0.850



50 bootstrap sample 250 bootstrap sample

Figure 8: Bootstrap Estimates for Cox regression Validation for Viral load data

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Ik ga akkoord,

Mubasiru-Asafe Lamidi

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