GBVDeterminants of Survival of HIV-HAART Naive Patients to HAART Initiation at Bondo Sub-County Hospital: A Two Year Retrospective Cohort Study.

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A Research Project submitted in partial fulfilment for the Award of a Degree of Masters of Science in Medical Statistics of The University of Nairobi

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DECLARATION

This project is my original work and has not been presented for a degree in any other university.

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DEDICATION

This research project is dedicated to my loving fiancée Stacy Juma, my son Eugene and family for their inspiration, support, encouragement and understanding throughout my study.

May God bless you.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immuno Deficiency Syndrome
ART	Antiretroviral Therapy
CCC	Comprehensive Care Centre
CD4+	Cluster of Differentiation 4
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
KNBS	Kenya National Bureau of Statistics
KNH	Kenyatta National Hospital
MOH	Ministry of Health
NACC	National Aids Control Council
NASCOP	National AIDS/STI Control Program
RNA	Ribonucleic acid
STI	Sexually Transmitted Infections
UON	University of Nairobi
WHO	World Health Organization

DEFINITION OF TERMS

HIV-HAART naïve: this is a new client enrolled into the patient care who has never been on antiretroviral therapy.

Patient survival: this is the time from patient admission in to the care program to the time the patient qualifies for HAART initiation.

Event: this is when the patient satisfies the set out HAART initiation criterion as per the HIV management guidelines.

Time to event: the dependent variable, measures the duration to the event defined by the status variable i.e. the time taken for the HIV-HAART naïve patient to qualify for HAART initiation.

ABSTRACT

HIV-AIDS remains a major public health issue in Kenya with a prevalence of 5.3% and contributing to 29% of annual mortality. Despite marked improvement in the provision for care and treatment a search for improvement of the current care and treatment programs will lead to better health outcomes.

Purpose: Various factors influence the prognosis of HIV disease however minimal research has been conducted to determine how the information gathered on enrollment influence the illness prognosis. The early identification of how this information can inform disease prognosis will aid in improving management strategies and increase quality of life of the HIV infected. The aim of this research was to determine how the collected information influence times to HAART eligibility and determine factors that influence this duration.

Materials and methods: The study was a retrospective cohort study that was carried out in the Bondo sub county hospital CCC. Primary data was collected from patient treatment files, in the period beginning January 2013 to December 2014 in to the data collection forms then entered into Microsoft excel, cleaned and transferred to Stata 13 for survival analysis.

Results: In the study period 2015 patients were enrolled and 164 (female=93, male =71) satisfied the inclusion and exclusion criteria. The medium survival time was 65days. The WHO stage of enrollment (p-value <0.0000) and age of enrollment (p-value 0.006) were found to be the major determinants of the time to HAART eligibility.

Discussion: The WHO stages of enrollment and age of enrollment were strongly associated with HIV prognosis and this could be attributed to level of immune status which is affected by both this factors.

Conclusion: Age of enrollment and WHO stage of enrollment were the main variables captured in MOH 257 that inform on HIV-HAART naïve disease progression to HAART eligibility.

Recommendation: This study needs to be done in a prospective study incorporating time dependent covariates so as to give a clear picture of the other covariates not picked in this study.

CHAPTER ONE: INTRODUCTION AND BACKGROUND TO THE STUDY

1.1 Introduction

1.1.1 Burden of Human Immunodeficiency Virus (HIV) infection

HIV is a lentivirus that causes HIV infection and leads to AIDs. The virus infects vital cells in the human immune system such as helper t-cells (specifically CD4 t cells) leading to progressive failure of immune system allowing for life threatening opportunistic infections and cancers to thrive.

The first case (National Aids Control Council kenya(NACC), 2014) of HIV in Kenya diagnosed in 1984 and since then the epidemic has evolved to be a major public health concern. Globally the WHO reports that (WHO, 2014) 36.9 million people are living with HIV most of whom are found in sub Saharan Africa where Kenya is. The HIV adult prevalence (National Aids Control Council kenya(NACC), 2014, p. 3) in Kenya by the year 2014 stands at 5.3%, adult being in reference to those fifteen years and above. Siaya County (Kenya National Bearau of Statistic(KNBS), 2013, p. 8) has a population of 842,304with a HIV prevalence (National Aids Control Council Kenya(NACC), 2014, p. 121) of 23.7%.Bondo sub county hospital is in Siaya County.

In Kenya, HIV remains a key public health issue, “the high burden of HIV and AIDS in Kenya accounts for an estimated 29% of annual deaths, 20% maternal mortality and 15% of deaths of children under 5 years of age” (National Aids Control Council Kenya(NACC), 2014).

Marked improvement has been made in the fight of HIV-AIDS with the introduction of highly active antiretroviral therapy(HAART) leading to 80% coverage of people living with HIV

requiring HAART (National Aids Control Council kenya(NACC), 2014, p. 21) despite this progress , HIV-AIDS still remains to be a major cause of mortality and morbidity in Kenya .

1.1.2 Management of HIV in Kenya

The points of entry in to care for HIV-AIDS management in the Kenya healthcare system (National Aids Control Council Kenya(NACC), 2014)include voluntary counseling and testing centers, prevention of mother to child testing points at the antenatal clinics, diagnostic testing and counseling centers in health care facilities at tuberculosis clinics and medical wards.

The HIV care program in Kenya takes care of enrolled patients in two categories (National AIDS/STI Control Program(NASCOP), 2011, p. 34) there are those who are enrolled on care and the others care and treatment. The care and treatment patients are those who are enrolled on HAART and cotrimoxazole prophylaxis therapy. Those on care are mainly on cotrimoxazole prophylaxis therapy since they are yet to satisfy the criteria for HAART initiation.

On being enrolled on HIV care the patient information is captured on a blue form known as MOH 257 which captures the patient basic information and is registered into the pre ART-register, MOH-316Aon subsequent visit the patient data is captured on this blue form.

1.1.3 Enrollment on care

On enrollment to the care facility critical information is collected from the patient and entered in to the blue card (MOH 257). This information includes:

- Patient profile: this is the bio data of the patient and includes their name, age, sex, contacts, marital status and a unique patient number.

- Patient source: this informs of where the patient has come from.
- Patient art history: informs of the ART history of the patient
- HIV status of family member: captures volunteered information of the patient concerning if there is anyone in their family with a history of HIV infection
- Art therapy: captures when patient is eligible for ART therapy and eligibility criterion.
- Visitation data: on subsequent visitation the patient information on weight, blood pressure, choice of family planning method for female, cotrimoxazole prophylaxis therapy and any laboratory investigation is captured.

1.1.4 Enrollment on care and treatment

The algorithm for adult enrollment onto care and treatment is that (NASCOP, 2014) is that all the below are initiated on HAART once counseled and found to be eligible for HAART initiation:-

- All HIV+ adults with a CD+4 counts of less than 500 irrespective of WHO stage.
- All HIV+ infected pregnant women
- All HIV+ infected breastfeeding women.
- All HIV+ infected spouses and sexual partners in sero-discordant relationships.
- All HIV+ infected adults with WHO stage 3 and 4
- All HIV+/hepatitis B virus co-infected adults
- All HIV+/TB co-infected adults

1.2 Problem statement

As seen above at patient enrollment there are those who do not qualify for HAART initiation and are thus put on care and followed up until when they satisfy the initiation criteria. Although in the long run all those diagnosed with HIV end up being initiated on HAART, lack of understanding of factors that influence the transition into requirement for HAART may lead to non-provision of non-optimal care. An understanding of how these factors influence the deterioration of the patients' immune system leading to the need to initiate HAART may inform policy and help tailor the kind of care provision which would identify the risk factors leading for the need for HAART.

At current the HIV program in Kenya is not able to ascertain whether the data collected on the blue card has information that influence the transition of the patients enrolled on care to their transition into the need for them being enrolled on HAART.

1.3. Study justification

The number of patient being initiated on HAART can be well forecasted and help in planning purposes if the factors accelerating the need to HAART are well identified. The patients who after assessment of factors that increase their rate to progress to HAART initiation criteria would therefore benefit from optimal tailored care. This would include proper adherence regimens; clinic dates that are informed by their factors and tailor made adherence counseling.

1.4 objectives of the study

1.4.1 Broad objective

To determine the progression (survival) of HIV -HAART naïve patients to the end point of when they satisfy the set out criterion for HAART initiation.

1.4.2 Specific objective

1. To determine the survival rate of HIV-HAART naïve patients to HAART initiation criterion using survival analysis.
2. To identify the risk factors that influence progression to HAART initiation criterion for HIV- HAART naïve patient using Cox regression model.
3. To ascertain if the variables captured in the MOH 257 are able to inform on HIV-HAART naïve disease progression to the HAART requiring end point.

1.5 Research question

(i) What were the survival rates in progression of HIV-HAART naïve patients to HAART initiation in Bondo district hospital in the period of 1stJanuary 2013 to 31st December 2014?

(ii) What are the variables captured in MOH 257 that inform on HIV-HAART naïve disease progression to the HAART requiring end point.

(iii) What are the risk factors that influence progression to HAART initiation criterion for HIV-HAART naïve patient using Cox regression model?

1.6 Hypothesis

1.6.1 Null Hypothesis

HIV–HAART naïve patient's survival to HAART eligibility is not affected by enrolment characteristics of the patient.

1.6.2 Alternative Hypothesis

HIV–HAART naïve patient's survival to HAART eligibility is affected by enrolment characteristics of the patient.

CHAPTER TWO: LITERATURE REVIEW

2.1 factors affecting HIV disease progression

During the extended clinically latent period associated with HIV infection the virus itself remains active and harmful to the body's various systems. This phase of infection leads to development of opportunistic infections which is the beginning of the symptomatic phase. Understanding the factors affecting the rate of progression to HAART initiation criterion (Simone, Jintana, & David, 2007) can aid treatment commencement and therapeutic monitoring decisions.

2.1.1 Age

Age at seroconversion has been found to impact on the progression of HIV. Age has been found to considerably correlate with CD4+cell count and HIV-RNA counts which have an impact on immune system status. There is a clear relationship between increasing risk of higher rates of disease progression with increase in age. (cascade collaboration, 2004).this raises the issue of whether or not older patients should be treated with a higher CD4+ cell counts a factor this study seeks to find out, especially in resource limited settings as is the case in Bondo.

Older age (Touloumi, Hatzakis, philip, thomas, & james, 1998) is associated with lower CD4 + cell counts at similar time from conversion which may explain the relation between age and disease progression. Although this study concentrated on hemophiliacs its findings could be extrapolated to the general population.

2.1.2 Gender

The mean HIV-RNA has been found to vary between men and women (Anastos , Gange , Lau , Weiser , & Detels , 2000, pp. 218-226) found that for a given CD4+ cell count strata. After

adjustment for differences in measurement method, baseline cd4 counts ,age, and clinical symptoms , HIV-1RNA levels were 32% to50% lower in women than men at cd4+ counts more than 200cells/mm3($p<.001$).

This could provide clues regarding this as a factor that influences HIV-disease progression in HAART-naïve patients and could provide information on how therapy should be adjusted for gender.

2.1.3 Body mass index

The body mass index (BMI) is a measure of nutritional status and its relationship to survival in HIV infection (Faauci & Lane, 2005, pp. 1076-1139)is important since a more than 10% involuntary weight loss in conjunction with chronic diarrhea and weakness is considered an AIDS defining illness as per CDC classification.

Long term monitoring of BMI is a cheap and easy monitoring indicator especially in resource limited settings. A weight loss study (Malvy , Thiébaut, Marimoutou, & Dabis , 2001, pp. 609-615) revealed that a weight loss greater than 10% tripled the risk of progression to clinical AIDS as compare to cases where there was no weight loss. Lower BMI values were associated with higher relative risk of disease progression in the same study.

2.1.4 Patient source

The entry point into a HIV-AIDS care provision center is dependent on where the patient is diagnosed. The relationship between this entry point and prognosis of the disease in the patient has not been established. Presumptively since patients diagnosed at heath care facility are likely to be already sick and thus of poor health, their prognosis is likely to compare poorly as compared to those whose entry is via a self-initiated volunteer counseling and testing centers point.

This study will seek to compare the outcome of this and inform therapy tailoring as per source of patient.

2.1.5 HIV status of family members

Efforts to expand access to HIV care and treatment often stresses the importance of disclosure of HIV status to aid in adherence, social support and more communal support. HIV-infected patients make strategic decision on who to disclose to their status (Winchester, et al., 2013, pp. 1253-1258). Disclosure is mainly to those physically and socially closest to them, this protects them from inadvertent disclosures by decreasing visible symptoms that make others aware of their symptoms. The limitation of this study though was that retrospective data on disclosure may not capture all early disclosure due to forgetting all they disclosed their status to.in this study the information on disclosure is capture on enrollment and thus has no recall challenge.

2.2 Summary of Review

The prognosis of HIV positive patients on care is affected by the various factors above, the degree and extent of each is what this study seeks to find out by way of survival analysis. The life table method is used to measure the survival rates of progression to HAART eligibility. The regression model assesses the effect of prognostic factors on the survival rate. The information gathered therein in to guide in tailoring of optimal treatment therapy for the benefits of the patient.

CHAPTER THREE: METHODOLOGY

3.1 Study design

The study was a retrospective cohort study of all HIV positive HAART naïve enrolled in to Bondo sub-county comprehensive care clinic. The study involved an analysis of the pre-art register from 1st January to 31st December 2014 for new enrollment and their time to satisfaction of HAART initiation criterion. This constituted their time to event and was the variable of interest. The patients who by end of the study had not satisfied criterion for HAART initiation were right censored.

3.2 Study area description

This study was conducted at the Bondo Sub-county hospital comprehensive care center (CCC). This is a sub county referral hospital serving what was formerly Bondo district and to a greater extent Rarieda sub-county. It has a bed capacity of 49 patients. It is situated in Bondo sub-county, Siaya County, in the Bondo Township. Bondo sub county hospital is a sub county referral hospital and also serves as a training hospital for the Kenya medical training college Bondo branch. The CCC serves patients from a greater part of the Siaya County but majority are from the Bondo Township and its environs. Bondo sub county(Kenya National Bearau of Statistic(KNBS), 2013, p. 5) has a catchment population of 157,522.

3.3 Study population

The study was conducted on all adult patients enrolled on care only at the Bondo sub county CCC in the period beginning 1st January 2013 to 31st December 2014. These patients were HAART naïve and receiving all the other aspect of comprehensive care except HAART.

3.4 Inclusion/Exclusion criteria

3.4.1 Inclusion criteria

All HIV+ HAART naïve adult patients enrolled in to the CCC in the period beginning 1st January 2013 to 31st December 2014 for care in the study period not satisfying HAART initiation criterion were enrolled in the study.

3.4.2 Exclusion criteria

All HIV+ HAART naïve adult patients enrolled in to the CCC for care in the period beginning 1st January 2013 to 31st December 2014 but satisfying HAART initiation criterion. HIV+ pregnant women and those co-infected with tuberculosis were excluded since in the current management guidelines (National AIDS/STI Control Program(NASCOP), 2011) they are initiated on HAART immediately on contact and after evaluation.

3.5 Sample size

The total number of patients enrolled at the CCC for the period January 2013 to December 2014 was 2015. This was a survival model and sampling was not required but rather the period of study and all those enrolled was of essence. The inclusion exclusion criterion was applied to this total enrolled to get the numbers for the study.

3.6 Data collection procedures

Data was obtained as primary data by trained research assistant from the pre- art register and the unique CCC number was used to draw the patient files from the registry. The file information was used to carry out the inclusion exclusion criteria to isolate the files that qualified for the study. The file that satisfied the inclusion criteria were selected and primary

data extracted from the MOH 257(blue card) into the study reporting tool. The data on the reporting tool was subsequently be entered into Microsoft excel.

3.7 Variables in the survival analysis

3.7.1 Event

This was the patient satisfying HAART enrolment eligibility.

3.7.2 Time to event

This variable measure was the duration of the event defined by the status variable. In this case this was the time taken to satisfaction of criterion for HAART initiation in days.

3.7.3 Status variable (outcome variable)

This was the event (HAART-Initiation) or not having satisfied the initiation criterion thus censored variable, this was as well the case for the patient lost to follow up in the study period. It was whether during the study period the patient was initiated on HAART, the(NASCOP, 2014) guidelines adhered to. At end of the period the observation time for those who had not satisfied HAART-initiation guidelines for initiation were censored.

3.7.4 Covariates

These were the independent variables which to be tested for association with the event of interest. These were of two types:

3.7.4.1 Categorical variables

These were factor variables covariate so will remain unchanged in the study period. This were Gender, patient source, HIV status of family member at enrollment, marital status at enrollment and WHO stage at enrollment.

3.7.4.2 Continuous covariate

These were age and the BMI at enrolment.

3.8 Training procedures

Five research assistants were recruited and trained to carry out the data extraction and entry..

3.9 Quality assurance

Double data entry was conducted.

The research assistants were trained to ensure quality data.

There was double entry of data into Microsoft Excel and entries compared.

3.10 Data collection instruments

Data extracted from the admission registers and inpatient records was entered into the data colleting tool and then transferred into Microsoft Excel

3.11 Data management plans

Data was entered into Microsoft excel and later transferred to Stata version13 to conduct the data analysis. Data cleaning was performed prior to analysis.

3.12 Data analysis

3.12.1 Survival Analysis

Survival analysis (Kleinbaum & Klein, 2005) is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs. For this study the event of interest is HAART-initiation.

3.12.2 Distribution of time to event

The event times obtained were analyzed to find their underlying distribution whether parametric or non-parametric. The measures of central tendencies of the survival time were also determined.

3.12.3 The survival function.

The survival function denoted S(t) is the probability that an individual survives longer than a specific time(t)

S(t) =P (an individual survives longer than time t)

=P (T>t)

T is a continuous random variable with probability density function (p.d.f.) f(t) and cumulative distribution function (c.d.f.) F(t) = P{T ≤ t}, giving the probability that the event has occurred by during time t. therefore

S(t) = P{T > t}= 1−F(t) = f(t)dt,

This gives the probability of being alive at duration t, or more generally, the probability that the event of interest has not occurred by duration t.

In our study the survival function S(t) will therefore be the probability that a patient has not been initiated on HAART at a time t which lies between the study time.

3.12.4 The hazard function

The hazard function h(t) is (Lee & wang, 2003, p. 25) probability of failure during a very small time interval, assuming that the individual has survived to the beginning of the interval. An alternative characterization of the distribution of T is by the hazard function H (t), or instantaneous rate of occurrence of the event.

$$h(t) = \lim_{\Delta t \longrightarrow 0} \frac{P(t \le T < t + \Delta t / T \ge t)}{\Delta t}$$

The numerator of the above expression is the conditional probability that the event will occur in the interval (t, t+ dt) given that it has not occurred before, and the denominator is the width of the interval. Dividing one by the other we obtain a rate of event occurrence per unit of time. Taking the limit down to zero, we obtain an instantaneous rate of occurrence.
In the study (t) will be the rate at which the HAART-naïve patients are initiated to HAART if there will be loss to follow up causing censoring.

3.12.5 Survival curves

The data obtained will be used to generate survival curves, in view that normally some patient will have been lost to follow up the Kaplan Meier (Kaplan & Meier, 1958) product limit method of estimating survivorship function will be employed.

Kaplan-Meier is used to estimate the survival curve without the assumption of an underlying probability distribution for survival times thus a non-parametric method. This method is based on the fact that the probability of surviving k or more times periods from joining the study is the product of survived survival rates for each period.

$S(k)=P_1*P_2*\ldots\ldots p_k$

Here P_1 is the proportion surviving the first period; P_2 is the proportion surviving beyond the second period as a condition and so on. The proportion surviving period *j* conditional on having survived up to period j is:

$$P_i= (n_j-d_j) \div n_j$$

Where $n_j$is the number HAART-naïve at the beginning of the period, d_j is the number who succumbs to our event of interest HAART-initiation.

The study fixed covariates survival curves will be generated by Kaplan-Meier method and the different groups within a covariate plotted e.g. the Kaplan-Meier survival curves for male and female patients enrolled in the time period.

The Kaplan-Meier curves will be mainly descriptive, will not control for covariates, will only use categorical predictors and will not accommodate the time-dependent variables

3.12.6 Comparison of survival within groups

In statistical comparison of two or more groups within a single fixed covariate variable the log rank test will be used. The log rank test (Mantel & Haenszel, 1959) tests whether or not Kaplan-Meier curves for two or more groups are statistically equivalent. It's a (Kleinbaum & Klein, 2005, p. 58) large sample chi-square test that uses observed verses expected cell counts over categories of outcomes.

The procedure (Machin, Campbell, & Walter, 2007)for calculating log rank test for two groups A and B:

I. The total numbers of events observed in groups A & B are O_A and O_B

II. Under the null hypothesis, the expected number of events in group A at time $t_i$is:

$$E_{Ai}=(d_i \, X \, n_{Ai}) \div n_i$$

t_i= ordered survival time.

E_{Ai}=expected number of events in group A.

d_i=number of events at t_i.

n_{Ai}=number at risk in group A.

III. The expected number of events should not be calculated beyond the last event.

IV. The total number of events expected on A, assuming the null hypothesis off no difference between 2groups is $E_{Ai}= \sum E_{Ai}$.

V. The number expected on group B is $E_B = \sum E_{Ai}$.

VI. to calculate the log rank $\chi^2 = ((O_A - E_A)^2 \div E_A) + ((O_B - E_B)^2 \div E_B)$

VII. the log rank χ^2 has a distribution with degree of freedom df=1 as two groups are being compared

3.12.7 Cox proportional hazard model

When the event time (Cox, 1972) underlying distribution is unknown the estimation and hypothesis testing of parameters in the models can conducted by applying standard asymptotic likelihood techniques. This model, the cox proportional hazard model (cox PH model) does not require knowledge of underlying distribution and its hazard function (Lee & wang, 2003, p. 298) can take any form but the hazard function of different individuals are assumed to be proportional and independent of time.

Key assumptions (Lee & wang, 2003) in the cox PH model are:

- The hazard of any individual is a fixed proportion of the hazard of any individual.
- The risks are multiplicative, that is the relationship between log cumulative Hazard and a covariate is linear.

In the cox PH model (Kleinbaum & Klein, 2005) has the baseline hazard function unspecified but must be positive and a linear set of fixed (time independent)covariates that are exponentiated as below:-

$$h_i(t) = \lambda_0(t) e^{\beta_1 x_{i1} + \ldots + \beta_k x_{ik}}$$

$$\log h_i(t) = \log \lambda_0(t) + \beta_1 x_{i1} + \ldots + \beta_k x_{ik}$$

The point of the model is to compare the hazard rates of individuals who have different covariates, hence called the proportional hazard

$$HR_{i,j} = \frac{h_i(t)}{h_j(t)} = \frac{\lambda_0(t)e^{\beta_1 x_{i1}+\ldots+\beta_k x_{ik}}}{\lambda_0(t)e^{\beta_1 x_{j1}+\ldots+\beta_k x_{jk}}} = e^{\beta_1(x_{i1}-x_{j1})+\ldots+\beta_1(x_{ik}-x_{jk})}$$

In this study the covariates to be tested for the proportion hazard will include marital status, gender, patient source and how they affect the rate to HAART initiation.

3.12.8 Model analysis and deviance

A test of the overall statistical significance of the model is given under the model analysis option. The likelihood chi square statistic will be calculated by comparing the deviance (-2*log likelihood of the model, with all the covariates you have specified, against the model with all the covariates dropped. The individual contribution of covariates to the model will assessed from the significance test given with each co efficient in the main output; this will assumes a reasonably large sample size. Deviance is minus twice the log of likelihood ratio for models fitted by maximum likelihood (cox 1972). The value of adding a parameter to a cox model is tested by subtracting the deviance of the model with a new parameter from the deviance of the model without the new parameter, the difference is then tested against a chi square distribution with degrees of freedom equal to the difference between the degrees of freedom of the old and new models. The model analysis option will tests the model specified against a model with only one parameter, the intercept; this will tests the combined value of the specified predictors / covariates in the model.

3.13 Ethical consideration

The study will make use of retrospective patient's records and there will be no contact with the patients. There will thus be no signing of the patient consent forms but instead ethical authority will be sought from the KNH-UON ethics and research committee for access of these records.

3.14 Limitations

The study is a retrospective study hence some relevant data may not have been recorded. I will ensure all the relevant available data is obtained.

CHAPTER FOUR: RESULTS AND ANALYSIS

4.1 Introduction

His chapter describes the analysis of data and the study findings

4.1.1 Study Design

The study was a retrospective 2 year cohort study of patients receiving care and treatment at Bondo Sub-county hospital between January 2013 and December 2014. The patient key data collected in the blue card of gender, age, body mass index, patient source, baseline CD+4 cell count, knowledge of family member HIV status, marital status, WHO stage on enrollment and the time to eligibility for HAART was collected.

4.1.2 Inclusion Exclusion Criteria

4.1.2.1 Inclusion

The patients enrolled in the period were 2015 and of this only 164 patient data satisfied the inclusion criteria s set up for the study.

4.1.2.2 Exclusion Criteria

The patients excluded from the study were 1850. Children were 288, whilst the others were adults 568 because they had comorbidity of tuberculosis and the rest 995 satisfied the set guidelines (NASCOP, 2014) for immediate initiation to HAART.

4.2 Baseline Enrollment Characteristics

A total of 164 patients satisfied the preset inclusion criteria for the study for the patients being enrolled at Bondo Sub-county hospital from January 2013 to December 2014.

4.2.1 Gender

The male constituted 43% while the female were 57%. All the observed patients during the period were eventually eligible for enrolled into HAART at study end time of December 2014.

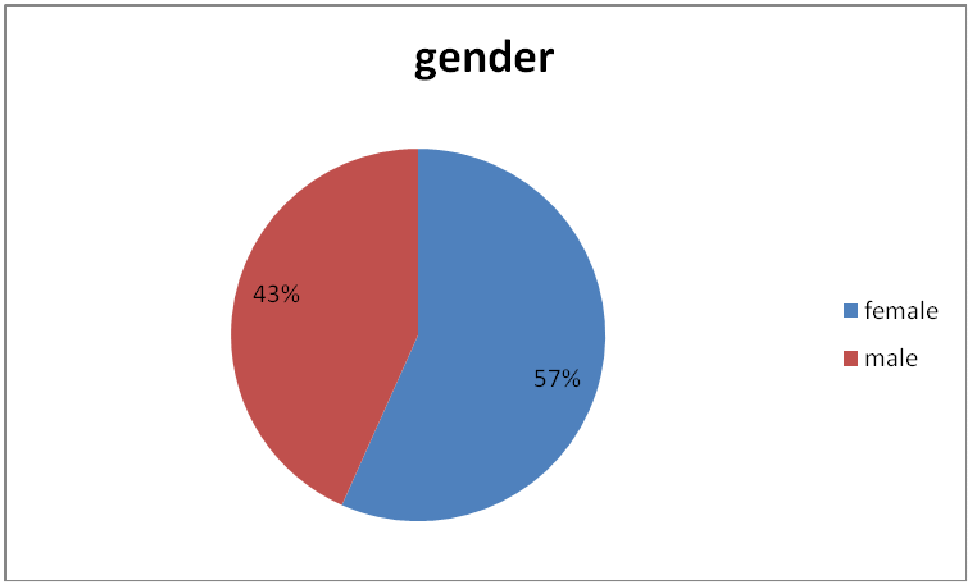

Figure 4. 1: Gender distribution at enrollment

4.2.2 Marital Status

At enrollment Majority of the enrolled patients were in a monogamous marriage 90, 29 were in a polygamous marriage, 5 were divorced, 2 were cohabiting with their partners, 12 were widowed and 26 of them were single

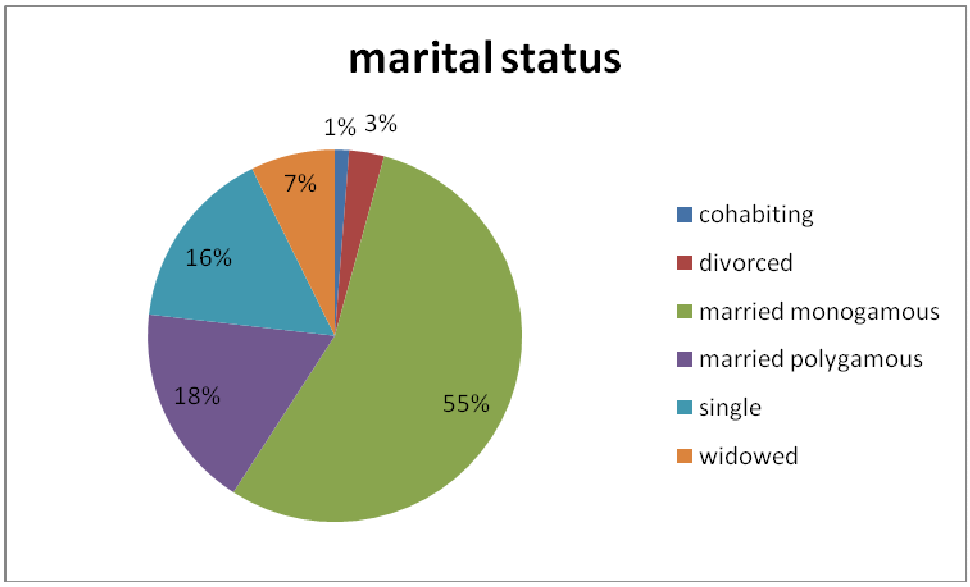

Figure 4.2: Marital status at enrollment

4.2.3 Patient Source

Patients coming to be enrolled were referred from the 3 entry points, 8 were referred from the in-patient diagnostic and testing point, 99 from the outpatient diagnostic testing center and 57 were from voluntary testing centers.

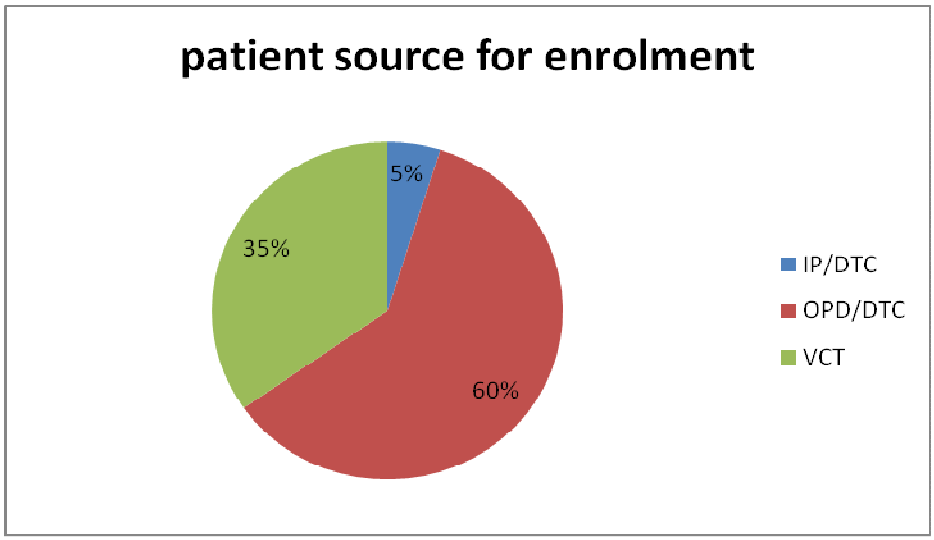

Figure 4. 3: Source of patient for enrolment to the care program

4.2.4 Knowledge of HIV status of Family Member

On enrollment the patient knowledge of a family member diagnosed with HIV showed that 107 of them had a known close family member with a confirmed HIV diagnosis while 57 had no knowledge of any family member with confirmed HIV status.

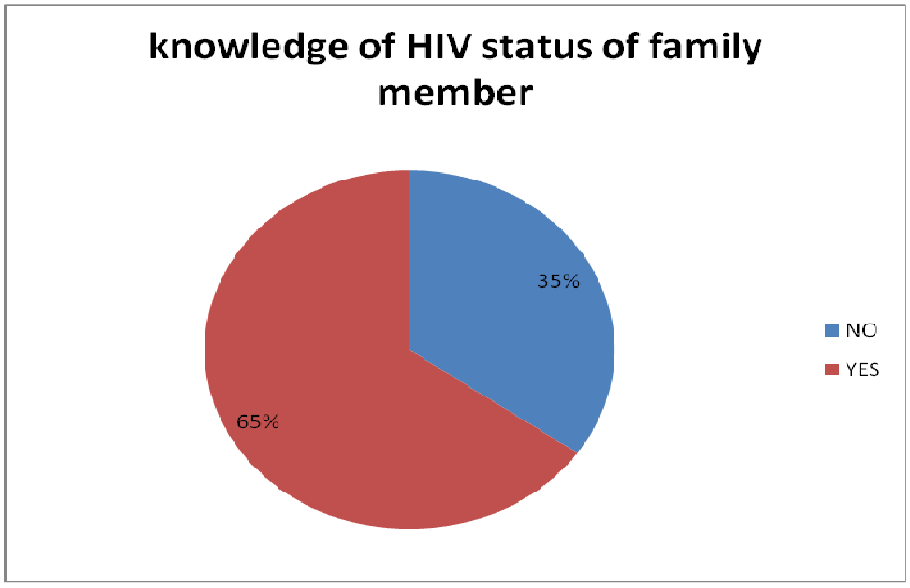

Figure 4..4: Knowledge of a family member diagnosed with HIV

4.2.5 WHO Stage at Enrollment

At enrollment the patients were assessed and classified as per WHO staging, 78 were found to be classified as being in WHO stage I and 84 were classified as WHO stage II.

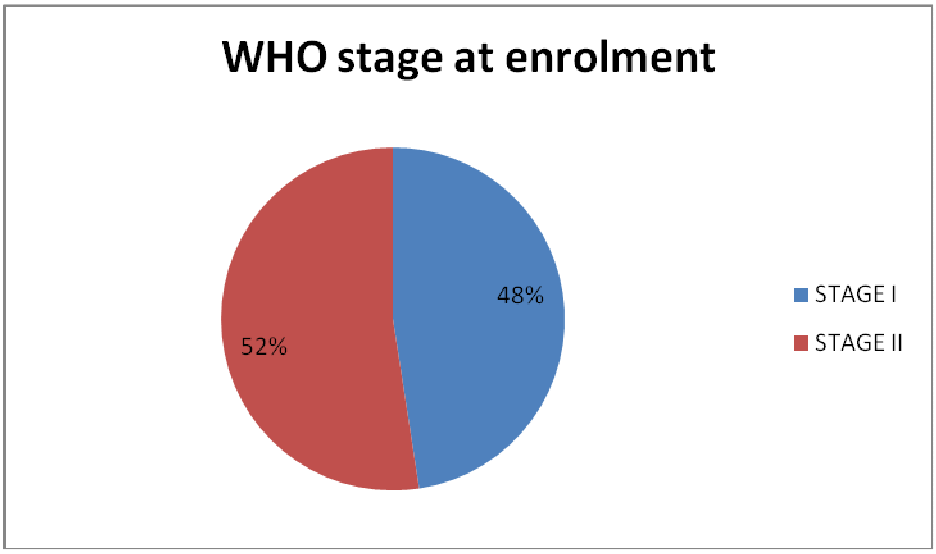

Figure 4.5: Knowledge of a family member diagnosed with HIV

4.2.6 Age at Enrollment

The mean age of enrollment during the study period was 36.78 with a standard deviation of 12.8. The means 95% confidence interval was [34.8, 38.75].

4.3 HIV positive HAART-naive patient's survival

A total of 164 patients were enrolled in the study and all at the end of the study had satisfied eligibility criteria for HAART initiation. The minimum exit time was 10 days, the median exit times was 65 days the maximum was 851 days with exit being satisfying eligibility to HAART. The 25^{th} percentile of survival time was 37 days and the 15^{th} percentile was 181 days.

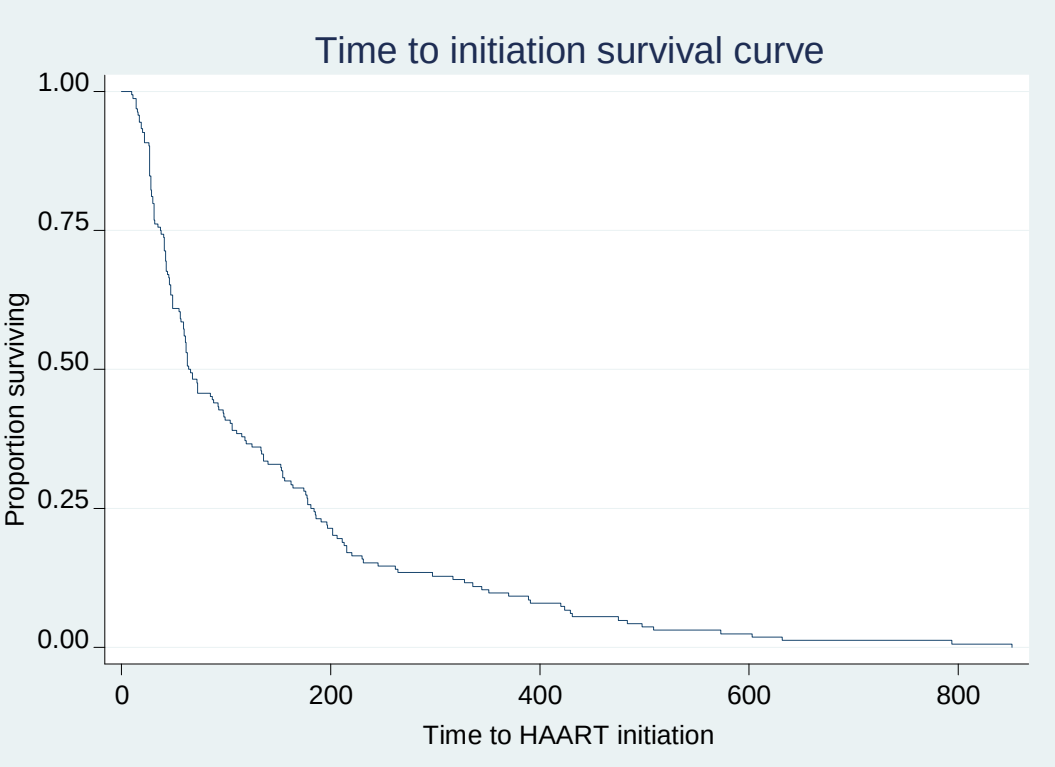

Figure 4. 6: Patient survival curve for all enrolled patients

4.4 Non Parametric test for Categorical variables

Kaplan Meier survival curves were used to analyze survival and the Wilcoxon (Breslow) test for equality of survivor functions was used to ascertain if there was significant difference in the survival distribution of the categorical variable. This was because it was observed that with a median of 65days it implied that event of interest appeared

4.4.1 Analysis for Gender

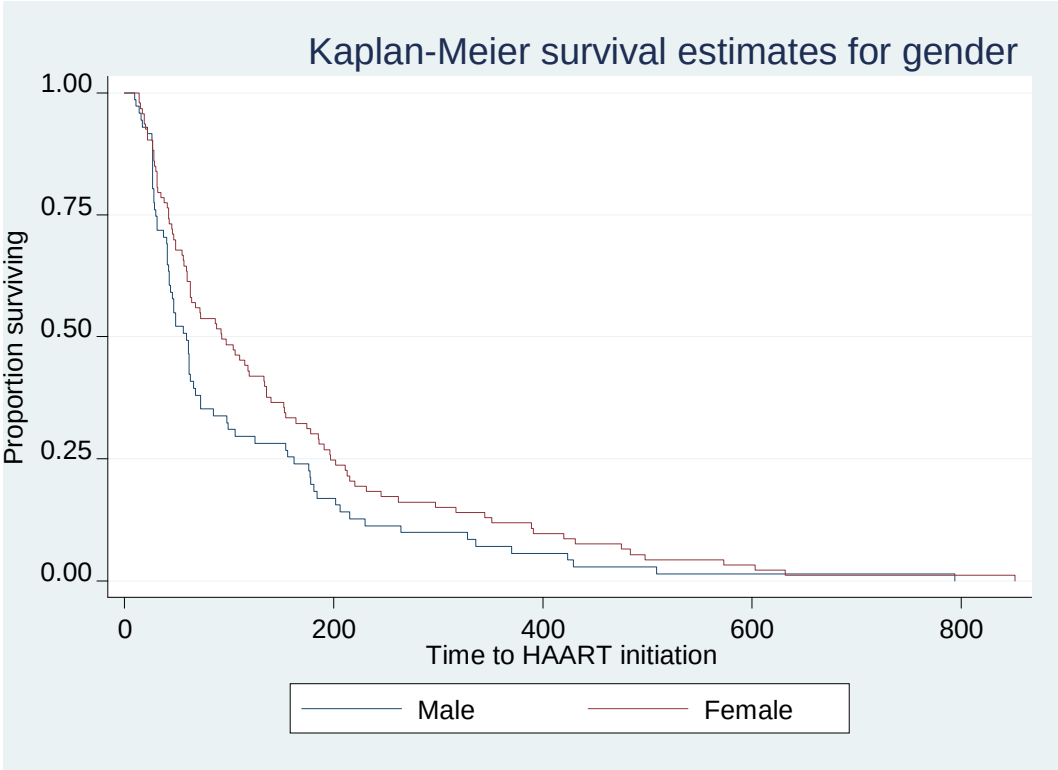

Figure 4.7: Kaplan Meier survival estimates for gender

Table 4. 1: Wilcoxon (Breslow) test for equality of survivor functions for gender

Gender	Events observed	Events expected	Sum of ranks
Male	71	59.54	1241
Female	93	104.46	-1241
Total	164	164	0

Chi2 (1) = 4.34 p-value=0.0275

This was statistically significant and would be included in the final model.

4.4.2 Analysis for marital status

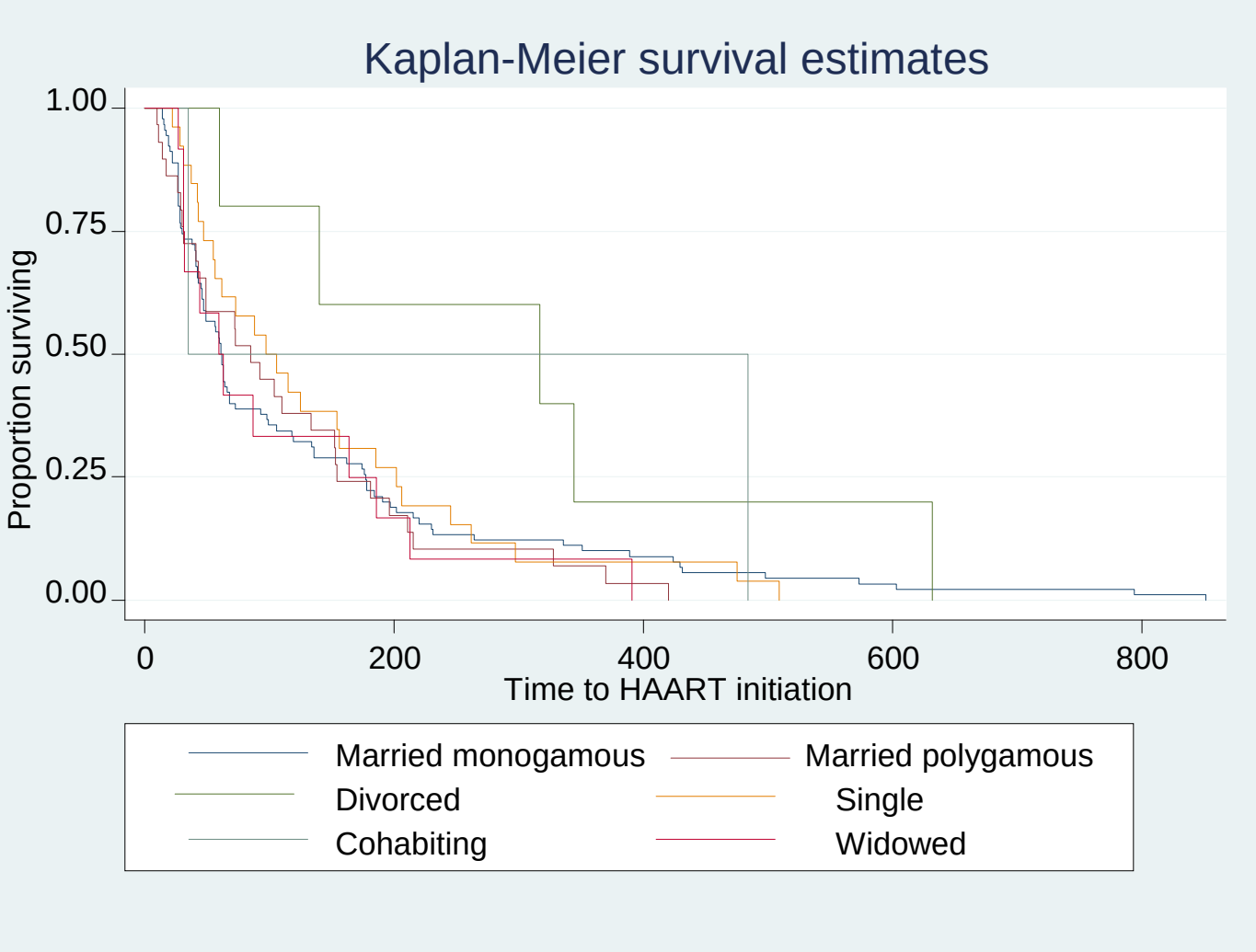

Figure 4.8: Kaplan Meier survival estimates for marital status

Table 4.2: Wilcoxon (Breslow) test for equality of survivor functions for marital status

Marital status	Events observed	Events expected	Sum of ranks
Married monogamous	90	86.85	840
Married polygamous	29	25.29	151
Divorced	5	10.15	-444
Single	26	28.17	-555
Cohabiting	2	3.35	-64
Widowed	12	1021	72
total	164	164	0

Chi2(5) = 5.69 p-value = 0.338

This was not statistically significant and would not be included in the final model.

4.4.3 Analysis for patient source

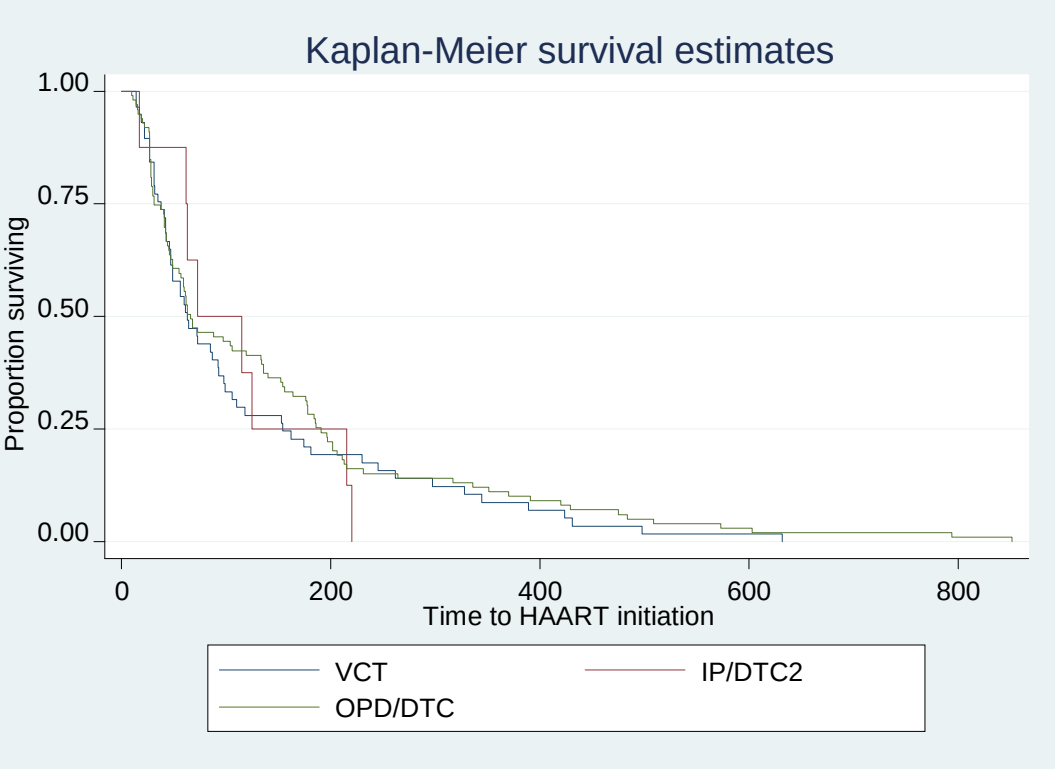

Figure 4.9: Kaplan Meier survival estimates for patient source.

Table 4.3: Wilcoxon (Breslow) test for equality of survivor functions for patient source

Patient source	Events observed	Events expected	Rank
VCT	57	52.58	336
IP/DTC	8	7.62	-143
OPD/DTC	99	103.8	-193
TOTAL	164	164	0

Chi(2) = 0.52 p-value = 0.7716

This was not statistically significant and would not be included in the final model.

4.4.4 Analysis for WHO stage at enrollment

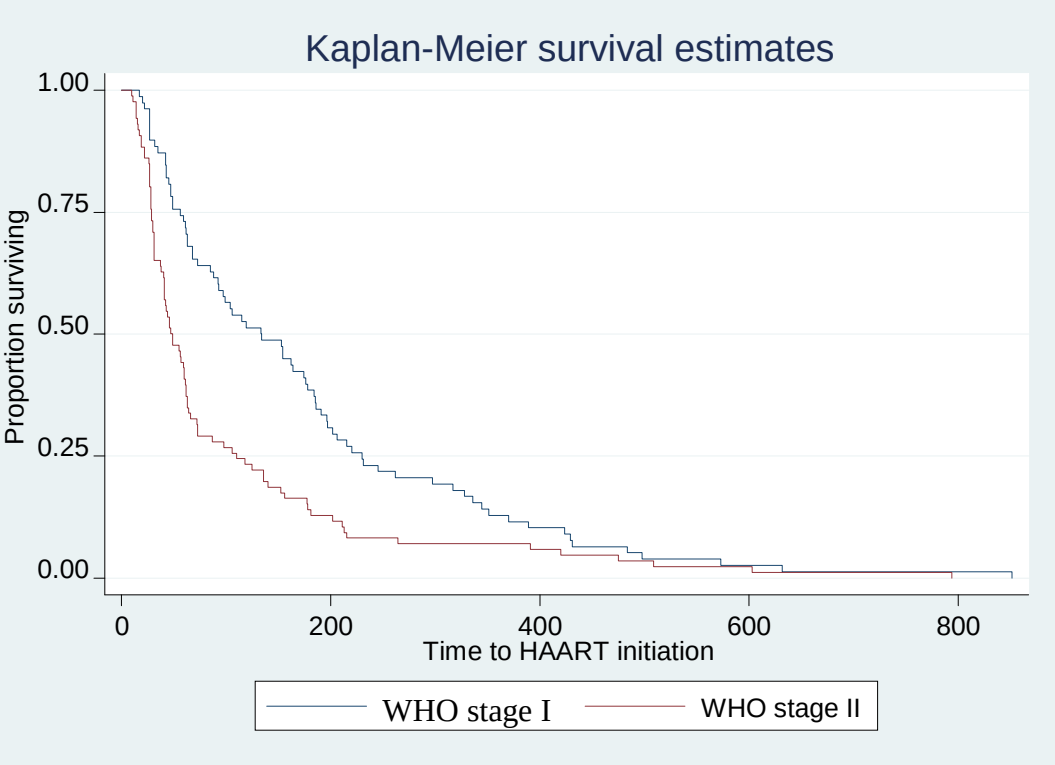

Figure 4.10: Kaplan Meier survival estimates for WHO stage at enrollment

Table 4.4: Kaplan Meier survival estimates for WHO stage

WHO stage	Events observed	Events expected	Rank
Stage I	78	100.44	-2760
Stage II	86	63.5	2760
Total	164	164	0

Chi2(1) = 21.10 p-value=< 0.0001

This was statistically significant and would be included in the final model.

4.4.5 Analysis for knowledge of diagnosed HIV+ family member

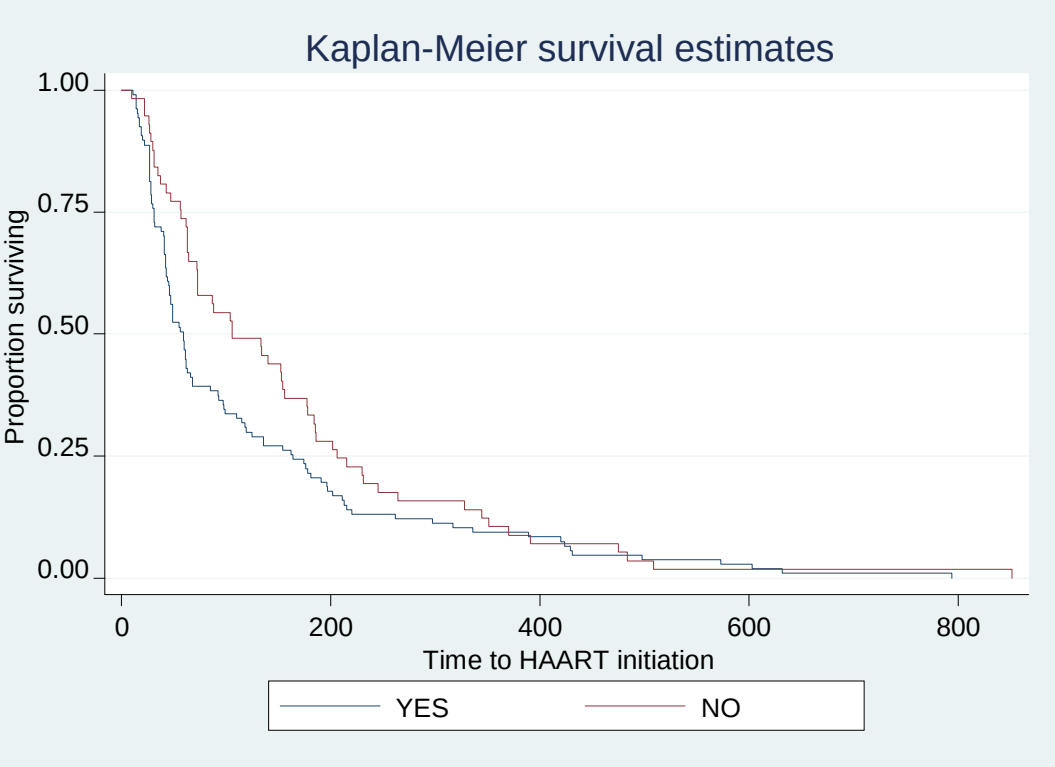

Figure 4.11: Kaplan Meier survival estimates for knowledge of diagnosed HIV+ family member

Table 4.5: Log rank for knowledge of diagnosed HIV+ family member

knowledge of diagnosed HIV+ family member	Events observed	Events expected	Rank
YES	107	95.7	1545
NO	57	63.3	-1545
Total	164	164	

Chi2(1) = 6.80 p-value=0.0091

This was statistically significant and would be included in the final model.

4.5 Cox proportional for Continuous variable

The data had 2 continuous variables taken at enrollment

4.5.1 Cox proportional hazard for age at enrollment

Cox regression was carried out with the ties handled by the Breslow method for ties.

Table 4.6.1: Cox regression output for age

_t	Hazard ratio	Standard error	z	P>IzI	[95%Confidence Interval	
Age	1.0195515	.0067639	2.91	0.004	1.006344	1.032859

Age at enrollment was considered for the final model since the p-value was 0.004 and was therefore statistically significant in influencing time to HAART initiation

4.5.2 Cox proportional hazard for BMI at enrollment.

Cox regression was carried out with the ties handled by the Breslow method for ties.

Table 4.6.2: Cox regression output for BMI

_t	Hazard ratio	Standard error	z	P>IzI	[95%Confidence Interval	
BMI	0.9991903	.001323	-0.61	0.542	0.9965922	1.001795

4.6 Model Building

The variables found to be significant were considered for the final model. These were gender, who stage at enrollment, knowledge of a family member with known HIV+ status and the age at enrollment.

4.6.1 Cox proportional hazard with all significant covariates.

The four variables found to be significant were fit in to a cox PH model and the findings were as below:

Table 4.6.3: Cox regression output for significant variables

_t	Hazard ratio	Standard error	z	P>IzI	[95%Confidence Interval	
Gender	0.8903265	0.1476927	-0.70	0.484	0.6432012	1.2324
Age at enrollment	1.016259	0.0068615	2.39	0.017	1.002899	1.029796
WHO stage at enrolment	1.696663	0.2727343	3.29	0.001	1.002899	1.029796
Knowledge of HIV+ family member	0.79708676	0.133139	-1.36	0.175	05745496	1.10582

The p-values for gender and knowledge of a family member with known HIV+ status were found to be non-significant and were eliminated in final model.

4.6.1 Cox proportional hazard fit model

After the first fitting the statistically significant covariates were incorporated in the final fit model and the findings were as below:

Table 4.6.4: Cox regression output for the final model

_t	Hazard ratio	Standard error	z	P>IzI	[95%Confidence Interval	
Age at enrollment	1.01798	0.0065841	2.76	0.006	1.005157	1.030966
WHO stage at enrolment	1.743588	0.27763384	3.49	0.000	1.276156	2.382232

CHAPTER FIVE: DISCUSSIONS

The findings of this study were that age of enrolment was a significant determinant of the time to HAART initiation on enrolment to care and treatment. The hazard ratio associated with age was 1.01798(p-value 0.006) which means that with every unit increase in age the increase in the rate of time to HAART initiation as per national guidelines is 1.8%. This may appear small but the public health burden of HIV-AIDS is large and the knowledge that older people have weak immunities and therefore suffer a higher rate of immune damage than corresponding younger ones should inform decision making. The results of this study were in agreement with the increasing risk of higher rates of disease progression with increase in age. (cascade collaboration, 2004). This raises the issue of whether or not older patients should be treated with a higher CD4+ cell counts a factor this study seeks to find out, especially in resource limited settings as is the case in Bondo.

The effect of marital status affection their progression to HAART initiation was found to be insignificant (p-value 0.338) and did not contribute to the final model. This can be explained by the fact that there have been a lot of behavior change initiatives aiming at dealing with stigma and formation of support groups that have changed population perceptions.

The study found significant difference in the time to HAART initiation between the male and female with the men having a higher rate of disease progression (p-value 0.0275) to needing HAART management. This was indifferent from the Previous laboratory studies have found that the mean HIV-RNA to vary between men and women (Anastos , Gange , Lau , Weiser , & Detels , 2000, pp. 218-226) for a given CD4+ cell count strata, after adjustment for differences in measurement method, baseline cd4 counts ,age, and clinical symptoms , HIV-1RNA levels

were 32% to50% lower in women than men at cd4+ counts more than 200cells/mm3($p<.001$). The effect of this findings were however not evident in our study that looked at the time to HAART as a dependent variable on gender. This could be explained by the fact that the sample had significantly more female than males and the better health seeking behavior of females in the catchment area.

The cox proportional hazard model with body mass index (BMI) was an insignificant fit (p-value-0.542) and as not included into the final model fit. It is a measure of nutritional status and its relationship to survival in HIV infection (Faauci & Lane, 2005, pp. 1076-1139) is important since a more than 10% involuntary weight loss in conjunction with chronic diarrhea and weakness is considered an AIDS defining illness as per CDC classification. This could be explained by the fact that our inclusion criteria only captured WHO stage I and II who generally have more manifestation of involuntary weight loss with chronic diarrhea.

The entry point into a HIV-AIDS care provision center was found to be of no significance (p-value 0.7716) to the time taken by enrolled patients to be eligible to HAART. The relationship between this entry point and prognosis of the disease in the patient was established to be not relating in the study.

Newly enrolled patient having prior knowledge of a known family member who has been diagnosed as being HIV+ had longer time to HAART eligibility (p-value 0.0091) compared to those who had no known family member. This though significant was found to be insignificant in the final cox proportional model. This was in agreement to the findings that HIV-infected patients make strategic decision on whom to disclose to their status (Winchester, et al., 2013, pp. 1253-1258) disclosure is mainly to those physically and socially closest to them, this

protects them from inadvertent disclosures by decreasing visible symptoms that make others aware of their symptoms.

The WHO stage of enrollment was found to be a significant determinant (p-value 0.0000) of the time to HAART eligibility with a significance .the patient enrolled with WHO stage II had 74% higher chance of faster progression to eligibility to HAART compared to those who were enrolled as WHO stage II in the final model fit.

CHAPTER SIX: CONCLUSION

6.1 Conclusion

In conclusion the main factors found to affect the time to HAART initiation for the patients enrolled at Bondo Sub-county hospital in the study period were age of enrollment and the WHO stage of enrolment.

Using Kaplan Meier and Cox regression we were able to come up with the following conclusion:

- The survival time to HAART eligibility was determined and risk factor of age of enrollment and patients WHO stage at enrolment were the main risk factors affecting progression to drug eligibility.
- Age of enrolment and WHO stage of enrollment were the main variables captured in MOH 257 that inform on HIV-HAART naïve disease progression to the HAART requiring end point
- The null hypothesis was rejected

6.2 Study Limitation

During the study period it was made aware that the ministry of health had implemented a Rapid Response Initiative (RRI) to increase the number of patients on HAART and this affected the true scenario as envisaged in the normal program undertakings. This explained the lack of patients for censoring at end of study and this affected the study findings.

Survival analysis requires reliable sources of data obtained from prospective cohort studies while we perform a retrospective design and use data recorded at the care site. The quality and

accuracy of the estimations and associations primarily depended on the quality of the recorded data, whereas we were unable to verify the accuracy of the data. This issue may raise possibility of information bias.

6.3 Recommendation

We recommend the Bondo Sub-county hospital for the complete filing up of MOH 257 which enabled the extraction of the relevant data for analysis.

This study needs to be done in a prospective study incorporating time dependent covariates so as to give a clear picture of the other covariates not picked in this study.

REFERENCES

National AIDS/STI Control Program(NASCOP). (2011). *Guidelines for aantiretroviral therapy in kenya.* Nairobi: NASCOP.

Anastos , k., Gange , S. J., Lau , B., Weiser , B., & Detels , R. (2000). Association of race and gender with HIV-1 RNA levels and immunologic progression. *journal of acquired immunodeficiency syndrome*, 218-226.

cascade collaboration. (2004). Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS 2004*, *18*(1), 51-58.

Cox, D. R. (1972). Regression Models and Lifetables. *Journal of Royal Statistical Society,* 187-220.

Faauci, A. S., & Lane, H. C. (2005). *Harrison's Principles of Internal Medicine 16 Edition (Edited by: Fauci AS, Lane HC). McGraw-Hill 2005, 1:p1076–1139.* McGraw-Hill 2005, 1:p1076–1139.

Kaplan, E. L., & Meier, P. (1958). Non-parametric Estimation from Incomplete Observation. *journal of American Statistical Association,* 457-481.

Kenya National Bearau of Statistic(KNBS). (2013). *statistical abstract 2013.* Nairobi: KNBS.

Kleinbaum, D. G., & Klein, M. (2005). *Survival analysis :a self learning text.* New York: springer.

Lee, E., & wang, J. W. (2003). *Statistical Methods for SUrvival Data Analysis.* New Jersey: John Wiley & Sons.

Machin, D., Campbell, M., & Walter, s. (2007). *A Textbook for the Health Sciences(Medical Statistics).* New Jersey: John Wiley & Sons.

Malvy , E., Thiébaut, R., Marimoutou, C., & Dabis , F. (2001). Weight loss and body mass index as predictors of HIV disease progression to AIDS in adults. Aquitaine cohort, France, 1985-1997. *journal of american college of nutrition*, 608-615.

Mantel, N., & Haenszel, W. (1959). Statistical Aspect of the Analysis of Data from Retrospetive Studies od Diseases. *Journal of National Cancer Institute*, 719-748.

NASCOP. (2014). *guidelines on use of ntiretroviral drugs for treating and preventing HIV infection:a rapid advise.* NAIROBI: MINISTRY OF HEALTH.

National Aids Control Council kenya(NACC). (2014). *kenya aids progressive report.* nairobi: natinal aids contol council.

National Aids Control Council Kenya(NACC). (2014). *KENYA HIV COUNTY PROFILES.* NAIROBI: National Aids Control Council Kenya.

Simone, L., Jintana, A., & David, C. (2007). Predictors of disease progression in HIV infection: a review. *AIDS Research and Therapy*, 11.

Touloumi, g., Hatzakis, a., philip, r., thomas, o., & james, g. (1998). Effects of age at seroconversion and baseline HIV RNA level on the loss of CD4+ cells among persons with hemophilia. *AIDS*, 1661-1667.

WHO. (2014). *GLOBAL UPDATE ON HEALTH SECTOR RESPONSE TO HIV*. GENEVA: WHO.

Winchester, M. S., McGrath, J. W., Kaawa-mafigiri, D., Namutiiba, F., Ssendegye, G., Nalwoga, A., et al. (2013). Early HIV disclosure and nondisclosure among men and women on antiretroviral treatment in Uganda. *AIDS Care: Psychological and Socio-medical Aspects of AIDS/HIV*, 1253-1258.

APPENDICES

APPENDIX I: SCHEDULE OF ACTIVITIES

Activity	July	August	September	October	November
Proposal Development					
Ethics approval					
Data collection					
Data entry and cleaning					
Data analysis					
Report writing					
Presentation of report					

APPENDIX II: BUDGET

Item	Description	Cost (KSH.)
Ethics approval	Payment to the Ethical Research Committee (ERC)	3,500
travel and accommodation	Travelling to Bondo and accommodation for 5days	20,000
Data collection tool	Printing of data collection tools	5000
Research assistant	Payment of 5 research assistant	Ksh. 1000 per day for 5 days=25,000
Stationary Pens Notebooks	5 pens @ Ksh. 30 2 notebooks @Ksh. 200	150 400
Subtotal		54,050
Miscellaneous	10% of the total expenses	5000
Total		59,050

APPENDIX III: DATA COLLECTION FORM

1. Patient profile

UNIQUE STUDY NUMBER				
SEX	MALE		FEMALE	
DATE OF BIRTH				
AGE				

2. MARITAL STATUS

MARRIED POLYGAMOUS		WIDOWED		COHABITING	
MARRIED MONOGAMOUS		DIVORCED		SINGLE	

3. PATIENT SOURCE

VCT	
IP/DTC	
OPD/DTC	

4. DATE OF ENROLLMENT INTO CARE…….

5. WHO-STAGE ON ENROLLMENT…….

6. HIV STATUS OF FAMILY MEMBER	SPOUSE	
	CHILD	
	PARENT	
	OTHER	

7. DATE OF ELLIGIBILITY TO ART……..

8. ELLIGIBILITY THROUGH

CLINICAL		CD4 + COUNT	
WHO-STAGE			

9. PATIENT ON COTRIMOXAZOLE PREVENTIVE THERAPY:

YES……NO…….

10. CLINIC VISITATION DATA

2013	J	F	M	A	M	J	J	A	S	O	N	D
DATE												
HEIGHT												
WEIGHT												

2014	J	F	M	A	M	J	J	A	S	O	N	D
DATE												
HEIGHT												
WEIGHT												

APPENDIX IV: PATIENT SURVIVAL TABLE

Time	Beginning total	fail	lost	Survivor function	Standard Error	[95%confidence interval]	
10	164	1	0	0.9939	.0061	0.9575	0.9991
11	163	1	0	0.9939	0.0086	0.9521	0.9969
14	162	3	0	0.9695	0.0134	0.9521	0.9872
15	159	1	0	0.9534	0.0147	0.9204	0.9834
16	158	1	0	0.9573	0.0158	0.9126	0.9794
17	157	2	0	0.9451	0.0178	0.8972	0.9711
19	155	2	0	0.9329	0.0195	0.8822	0.9623
20	153	1	0	0.9268	0.0203	0.8747	0.9578
22	152	3	0	0.9085	0.0225	0.8529	0.9438
26	149	1	0	0.9024	0.0232	0.8457	0.9391
27	148	9	0	0.8476	0.0281	0.7828	0.8943
28	139	4	0	0.8232	0.0298	0.7556	0.8736
29	135	2	0	0.811	0.0306	0.7422	0.8631
0	133	2	0	0.7988	0.0313	07289	0.8525
31	131	5	0	0.683	0.0329	0.6959	0.8256
32	126	1	0	0.7622	0.0332	0.6893	0.8202
35	125	1	0	0.7561	0.0335	0.6828	0.814
37	124	1	0	0.75	0.338	0.6793	0.8093
38	123	1	0	0.7439	0.0341	0.6698	0.8038
40	122	1	0	0.7378	0.0343	0.6633	0.7983
41	121	4	00	0.7134	0.0353	0.6376	0.7762
42	117	3	0	0.6951	0.0359	0.6184	0.7594
43	114	3	0	0.6768	0.0365	0.5994	0.7425
44	111	1	0	0.6707	0.0367	0.5931	0.7369
45	110	1	0	0.6646	0.0369	0.5868	0.7312
46	109	2	0	0.652	0.0372	0.5742	0.7198
47	107	3	0	0.6341	0.0376	0.5555	0.7027
49	104	1	0	0.6098	0.0381	0.5307	0.6798
55	100	1	0	0.6037	0.0382	0.5245	0.6738
56	99	2	0	0.5915	0.0384	0.5122	0.6622
57	97	1	0	0.5854	0.0385	0.5060	0.6564
59	96	2	0	0.5732	0.0386	0.4938	0.6447
60	94	2	0	0.5610	0.0388	0.4816	0.6329
61	92	2	00	0.5488	0.0389	0.4694	0.6212
62	90	3	0	0.5305	0.0390	0.4513	0.6034
63	87	4	0	0.561	0.0390	0.4273	0.5796
64	83	1	0	0.5000	0.0390	0.4213	0.5736
66	81	1	0	0.4939	0.0390	0.4153	0.5676
68.	81	2	0	0.4817	0.0390	0.4034	0.5556
72	79	1	00	0.4756	0.039	0.3975	0.5496

73	78	3	00	0.45730	0.0389	0.3798	0.5314
85	75	1	0	0.4512	0.0389	0.3739	0.5326
87	74	1	0	0.4451	0.0388	0.3680	0.5121
88	73	1	0	0.4390	0.0388	0.3621	0.5132
92	72	1	0	0.4329	0.0387	0.3563	0.5017
93	71	1	0	0.4268	0.0386	0.3504	0.5009
97	070	1	0	0.4207	0.0385	0.3446	0.4984
98	69	1	0	0.4146	0.0385	0.3388	0.4887
99	68	1	0	0.4085	0.0384	0.3330	0.4825
104	67	1	0	0.424	0.0383	0.3272	0.4764
106	66	2	0	0.3902	0.0381	0.3156	0.4640
110	64	1	0	0.3841	0.0380	0.3099	0.4578
115	63	1	0	0.3780	0.079	0.3041	0.4454
118	62	1	0	0.372	0.0377	0.2984	0.4391
119	61	1	0	0.3659	0.0376	0.2927	0.4329
125	60	1	0	0.3598	0.0375	0.287	0.4266
133	59	1	0	0.3537	0.0373	02813	0.4204
134	58	1	0	0.3476	0.0372	0.2756	0.4078
136	57	2	0	0.3354	0.0369	0.2343	0.4014
140	55	1	0	0.3293	0.0367	0.2587	0.4015
152	54	1	0	0.3232	0.0365	0.2530	0.3952
153	53	1	0	0.3171	0.0363	0.2474	0.3888
154	52	2	0	0.3049	0.0359	0.2362	0.3761
156	50	1	0	0.2988	0.0357	0.2307	0.3697
162	49	1	0	0.2927	0.0355	0.2251	0.3634
164	48	1	00	0.2866	0.0353	0.2196	0.3570
174	47	1	000	0.2805	0.0351	0.2140	0.3505
176	46	1	00	0.2744	0.0348	0.2085	0.3441
177	45	1	00	0.2683	0.0346	0.2030	0.3377
178	44	2	00	0.2561	0.0341	0.190	0.3247
181	42	1	0	0.2500	0.0338	0.1867	0.3182
184	41	1	0	0.2439	0.0335	0.1812	0.3117
185	40	1	0	0.2378	0.0332	0.1758	0.3052
186	39	1	0	0.2317	0.0329	0.1705	0.2986
191	38	1	0	0.2256	00326	0.1651	0.2921
196	37	1	0	0.2195	0.0323	0.1597	0.2855
197	36	1	00	0.2134	0.0320	0.1544	0.2789
202	35	21	0	0.2012	0.0313	0.1438	0.2656
206	33	1	0	0.1951	0.0309	0.1386	0.2590
211	32	1	0	0.1890	0.0306	0.1333	0.2523
213	31	1	0	0.1829	0.0302	0.1281	0.2456
215	30	2	0	0.1707	0.0294	0.1177	0.2321
220	28	1	0	0.1646	0.0290	0.1126	0.2253
230	27	1	0	0.1585	0.0285	0.1075	0.2185
231	26	1	0	0.1524	0.0281	0.1024	0.2117
245	25	1	000	0.1463	0.0276	0.0974	0.2048
245	25	1	0	0.1463	0.0276	0.0974	0.2048
262	24	1	0	0.1402	0.0271	0.0923	0.1980

264	23	1	0	0.1341	0.0266	0.0873	0.1910
297	22	1	0	0.1280	0.0261	0.0824	0.1841
317	21	1	0	0.1220	0.0256	0.0775	0.1771
328	20	1	0	0.1159	0.0250	0.0726	0.1701
336	19	1	0	0.1098	0.0244	0.0678	0.1630
344	18	1	0	0.1037	0.0238	0.0630	0.1559
351	17	1	0	0.0976	0.0232	0.0583	0.1488
370	16	1	0	0.0915	0.0225	0.0536	0.1461
389	15	1	0	0.0854	0.0218	0.0490	0.1343
391	14	1	0	0.793	0.0211	0.0444	0.1270
420	13	1	0	0.07320	0.0203	0.0399	0.1122
424	12	1	0	0.0671	0.0195	0.0355	0.1047
429	11	1	0	0.061	0.0187	0.0312	0.0971
431	10	1	0	0.0549	0.0178	0.0270	0.0894
475	9	1	0	0.0488	0.0168	0.0229	0.0816
48	8	1	0	0.427	0.0158	0.0189	0.0736
498	7	1	0	0.0366	0.0147	0.0816	0.0645
509	6	1	0	0.0305	0.0134	0.0739	0.0655
573	5	1	0	0.0244	0.0120	0.0081	0.0572
603	4	1	0	0.0183	0.0105	0.0050	0.0486
632	3	1	0	0.0122	0.0086	0.0024	0.0398
794	2	1	0	0.0061	0.0061	.0006	0.0309
851	1	1	0	0.0000			

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