PREDICTORS OF EARLY MORTALITY IN HIV INFECTED PATIENTS STARTING 1ST LINE ART

Presented by

Peter Kipkurui Yegon

Registration Number W62/65321/10

As part of fulfillment of a degree of Master of Science in Medical Statistics of the University of Nairobi.

Through

Institute of Tropical and Infectious Diseases, College of Health Sciences (UNITID)

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Declaration

This project is my original work and has not been submitted for a degree in any other university. No part of this work maybe reproduced without permission of the University of Nairobi.

Peter Kipkurui Yegon , Registration W62/65321/10

Date_____Signature_____

Recommendation

A: This project has been submitted with our approval as protocol team members and as supervisors at KEMRI/ Walter Reed Project Kericho.

1. Dr. Douglas N Shaffer, Protocol Principal Investigator CLADE study

   Date _____Signature_____

2. Prof. Samwel Sinei, Investigator CLADE study and MSc mentor

   Date _____Signature_____

B: This project has been submitted with our approval as University of Nairobi project supervisors

1. Mr. Thaddeus Egondi – Project supervisor

   Date _____ Signature _____

2. Mrs. Ann Wangombe – Course coordinator and project supervisor

   Date_____Signature _____

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I would also like to acknowledge my family for their support as I juggled between all these many responsibilities sometimes using personal / family time to meet all the demands. I cannot forget the study participants who made the study possible through their willingness and consenting to participate.

Dedication

This work is dedicated to my beloved family, wife – Irene & sons Bradley, Eddie and Curtis.

Project Team and Affiliations

Project Presented by

Peter Kipkurui Yegon

Registration: W62/65321/10

Master of Science in Medical Statistics

University of Nairobi School of Health Sciences

Institute of Tropical and Infectious Diseases (UNITID)

Project Supervisors

A: KEMRI/ Walter Reed Project

1. Dr. Douglas N Shaffer - KEMRI/WRP HIV Program and Principal Investigator CLADE Protocol (Overall project supervisor)
2. Dr. Jonah Maswai – CO PI CLADE study KEMRI/ WRP HIV Program
3. Prof. Samwel Sinei- KEMRI/WRP HIV Program MSc Program Supervisor/Mentor

B: University of Nairobi Institute of Tropical and Infectious Diseases (UNITID)

1. Prof. B Estambale- UNITID Director
2. Mr. Thaddeus Egondi- Project Supervisor
3. Mrs. Ann Wangombe – Course Coordinator and Project Supervisor

Abstract

Despite widespread Antiretroviral Therapy (ART) availability, patients put on treatment suffer early mortality due to a number of factors. The Clinic-based ART Diagnostic Evaluation (CLADE) study is an open label, randomized control trial (RCT) evaluating feasibility and superiority of 2 ART treatment monitoring approaches in treatment-naïve adults in district-level, non-research clinics in rural Kenya. A secondary objective is to examine baseline characteristics and mortality outcomes. Descriptive summary statistics and multivariate logistic regression (RR, 95% CI) are used to evaluate baseline characteristics and relationships with 6 month mortality.

820 adults were enrolled in the study (57.6% female, Mean age=37.6 (SD 9.0) years) with advanced disease: Mean CD4 count =166 (SD106) cells/mm^3, Mean Viral Load = 231,901 (SD 246,242) copies/ml, WHO Stage III or IV= 28.8%, and Body Mass Index (BMI) <18.5=23.3%. 818 (99.7%) of those enrolled started ART treatment and were followed up in the study. Overall there were 70 deaths in the study (8.6%), the majority occurring within 6 months of initiating ART (80.0 %,). There was no significant study Arm differences (p=0.1) at 6 months.

Univariate Logistic regression showed CD4 count (p<0.0001), Viral Load (p=0.006), World Health Organization (WHO) Staging (p<0.0001), Body Mass Index (BMI p<0.0001) and Hemoglobin (Hgb p=0.005) were independently associated with early mortality. In Multivariate analysis WHO staging (p=0.045) and Hemoglobin (Hgb p=0.023) levels were the only significant factors predicting early mortality controlling for CD4 count result, viral load and Body Mass Index (BMI).

Early Mortality still remains a challenge in HIV positive patients starting ART in rural clinics of South Rift Valley, Kenya. However this can be reduced by early HIV diagnosis and early initiation of ART treatment. Intervention measures to deal with malnutrition and anemia need to be put in place to improve survival.

Hypothesis

Socio-demographic characteristics (variables) exist among adults starting 1st line ART that have predictive Early Mortality.

Objectives

a) **Primary Objective**
   To use regression analysis to estimate relative risk for early mortality for given baseline characteristics.

b) **Secondary Objectives**

1. Identify cases of early mortality among a cohort of 818 adults starting 1st line ART.
2. Compare baseline characteristics between those who experience early mortality and those continuing the study follow ups at six months.
3. To generate a Kaplan Meier Survival curve based on the six month follow up data.

Introduction

The Global Incidence of HIV Infection has stabilized and beginning to decline in countries with generalized epidemics. The Number of people receiving antiretroviral therapy continues to increase, with 6.65 million people getting treatment at the end of 2010. Recent published evidence from clinical trials has confirmed the powerful impact antiretroviral drugs have on the epidemic as part of an effective package of options for HIV prevention. Despite these advances, still too many people are acquiring HIV infection, too many people are getting sick and too many people are dying. Key challenges remain to be addressed. Most people living with HIV (PLWH) are not aware of their HIV status, and in most settings, PLWH access ART at an advanced stage of HIV disease, contributing to mortality and morbidity and missed prevention opportunities [1.] As access to treatment has expanded, the number of AIDS-related deaths has declined substantially. In modeling of the epidemic both with and without ART, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that ART has averted 2.5 million deaths in Low and middle income countries(LMICs) since 1995 with the most deaths averted in sub-Saharan Africa, where approximately 1.8 million lives have been extended as a result of treatment [1]. In sub-Saharan Africa, where AIDS-related deaths peaked in 2005 at 2.2 million, UNAIDS estimates that fewer people (460,000; 30%) died in 2010. In a recent study that compared mortality in Presidents Emergency Plan for Aids Relief (PEPFAR) focus countries which were most severely affected with HIV/AIDS and received more PEPFAR resources in Africa versus non-focus countries, persons living in focus countries had 19.8% lower odds of death in the period from 2003 to 2008 when compared with those living in non-focus countries [2.] Another analysis utilizing data

from UNAIDS and from demographic health surveys from 2004 to 2007 showed a significant decrease in HIV- and AIDS-related deaths in PEPFAR focus countries after 4 years of implementation as compared with other African countries [3.]

The South Rift Valley of Kenya where the study was conducted has a number of Government of Kenya (GOK) and Faith based hospitals as well as private hospitals being supported by PEPFAR funds through the Kenya Medical Research Institute /Walter Reed project (KEMRI/WRP) to offer care and treatment to HIV clients improving term survival and reducing early mortality from HIV.

Background Information

1. HIV AIDs in Kenya and the South Rift Valley province

HIV/AIDS remains in epidemic proportion throughout much of Sub-Saharan Africa and with significant impact worldwide. According to Kenya National Bureau of statistics 2010, Kenya's population was 38.6 million based on 2009 census report. As at December 2011, 1.6 million were living with HIV AIDS. HIV infected individuals are now living longer as a result of increased treatment access. HIV prevalence in 2010 was 6.2% which was 40% lower than the epidemics peak. An estimated 49 126 people died of AIDS causes in 2011, slightly more than one third the number who died in 2002-2004. Important gains have been made in preventing new HIV infections with Kenya having one of the words highest coverage rates of services to prevent mother to child HIV transmission with 69% of HIV positive pregnant women receiving antiretroviral prophylaxis in 2011. Kenya is also a global leader in scaling up of voluntary medical male circumcision as well as other biomedical interventions known to reduce HIV transmission. In HIV treatment, the country has made gains in delivering life preserving treatment to people living with HIV contributing to a notable reduction in AIDs related

deaths. In 2011 83.1% of adults who were eligible for antiretroviral therapy were receiving it. Antiretroviral coverage is still low for children (31.1%) although pediatric antiretroviral treatment coverage is also on the rise. In response to evidence demonstrating the health benefits of earlier therapy, Kenya has revised its adult treatment guidelines to raise CD4 count threshold for initiating therapy from 250 cells/mm^3 to 350 cells /mm^3 .

The sustainability of Kenya's care and treatment initiatives, as well as biomedical interventions for HIV prevention that are delivered in clinical settings, will depend on the strength of the country's health system. Major improvements have been made in the quality and distribution of health services in Kenya since 2004, although basic health indicators offer a mixed picture regarding the impact of these reforms. The epidemic's future in Kenya will be determined, in large measure, by the country's success in attracting the resources needed to continuing scaling up essential services. According to a modeling exercise undertaken by Futures Institute, continuing Kenya's push to achieve universal access to HIV prevention, treatment, care and support would result in 57% fewer new HIV infections in 2030 than in 2005, lower AIDS-related deaths by 41%, and reduce HIV prevalence by more than 60%. Refocusing limited resources on the especially cost-effective interventions would reduce the number of new infections by 45% and the number of AIDS-related deaths by 34%. [4.]

The South Rift Valley where the study was conducted consists of 4 counties (Nandi, Kericho, Bomet and Narok) out of the 15 counties in the whole of Rift Valley province of

Kenya. According to the 2009 Kenya census report population of Nandi County was reported at 752,965, Kericho county 758,339, Bomet 724,186 and Narok county 850,920: Which is a combined total population of 3 million Kenyans in the catchment area. [5.] Kenya Aids Indicator Survey (KAIS) 2007 reported a 7.4 % HIV prevalence in the whole of Rift valley province which is close to the national figure of 7.8% for the same period. [6.]

The Presidents Emergency Plan for Aids Relief (PEPFAR) program / KEMRI-WRP supports over 100 treatment sites in the South Rift Valley and has the largest and most successful prevention of mother to child transmission (PMTCT) program in the region with over 400 facilities offering the service. The treatment sites are satellites of 11 treatment partners consisting of 7 Ministry of Health (MOH), 2 faith-based (Mission) and 2 tea plantation hospitals (private) spread across Nandi County in North Rift Valley, 3 South Rift valley counties of Narok, Kericho and Bomet. Integrated to the treatment sites are a number of HIV prevention programs that offer counseling and testing as well as biomedical prevention strategies like Voluntary Medical Male circumcision program targeting non circumcising communities within the area of operation.

As of March 2012, Care and treatment program had registered over 50,000 clients in HIV clinics in the South Rift Valley with 50% of these being put on Highly Active Antiretroviral Treatment (HAART), the PMTCT program reached 484,965 new ANC clients with 15,257 (3.5%) testing HIV positive in the same period. Tuberculosis is known to be a major problem on HIV treatment contributing to most mortality cases being experienced. To provide mitigation to this the South Rift valley treatment program

has worked on integrating TB and HIV care and treatment services as per the Kenya national guidelines. The program has an intensive case finding model both in the clinic and at community level using the Intensive Case finding (ICF) TB screening tools. The HIV and TB treatment integration has been successful in the region as described by Shaffer et al "Successes and Challenges in an Integrated Tuberculosis/HIV Clinic in a Rural, Resource-Limited Setting: Experiences from Kericho, Kenya". Operational components of the integrated TB/HIV clinic included

(1) HIV Diagnostic Testing and Counseling (DTC) for patients and family members presenting to the TB clinic where >90% annual patient acceptance rate was achieved.

(2) Use of "cough monitors" (trained lay individuals) to maximize sputum collection in an effort to improve case finding and categorization of TB disease.

(3) Referral to the TB clinic of all patients diagnosed with TB in the HIV clinic

(4) Treatment for HIV including ART in the TB clinic with patient referral for continued care to the HIV clinic on completion of TB therapy. [7.]

2. Justification of the study

In Kenya HIV AIDS still contributes a substantial number of mortality cases despite the availability of ART. With declines in HIV prevalence, there has been an increase in the mortality rate and reduced life expectancy over the past 15 years (1994-2009). Between 1998 and 2003, the mortality rate increased by 40% among women and 30% among men aged 15-49 (KDHS 1998 and KDHS 2003). According to the National STIs Control Program (NASCOP), the number of deaths attributed to AIDS peaked in 2003 at 120,000, dropping to 85,000 by 2007. [8.]

Table I below shows the annual deaths for year 2011 as 57,000 (range 48,000- 66,000). According to National HIV estimates for 2011 a Spectrum model can be used to estimate the impact of treatment in terms of the number of lives saved. An estimated 230,000 AIDS deaths have been avoided through 2010 due to the scale-up of ART. [9.]

Table I: Kenya annual statistics for 2011

Indicator	**Value**	**Range**
Number Living with HIV	1,600,000	1.5 – 1.7 million
New adult infections	98,000	82,000 - 120,000
Mothers needing PMTCT	87,000	75,000 – 100,000
Annual AIDS deaths	57,000	48,000 – 66,000

Since the epidemic began, HIV has claimed the lives of at least 1.7 million people in Kenya. In 2011, an estimated 49,126 people in Kenya died of AIDS-related causes. The AIDS death toll in 2010 represents a nearly two-thirds drop from the peak in AIDS deaths in 2002–2004, when an estimated 130,000 people died each year. [10.]

CLADE Study Design

"**CL**inic-based **A**RT **D**iagnostic **E**valuation" (CLADE) is an unblinded, randomized (1:1), prospective, observational, cohort public health evaluation (PHE) aimed at evaluating the superiority and cost-effectiveness of two recommended Ministry of Health (MoH) ART diagnostic evaluation approaches at the clinic level in adult treatment naive patients beginning MoH approved first-line ART: "routine care," the most common approach to ART roll-out where clinical (World Health Organization (WHO) staging and immunological (CD4) monitoring are the primary baseline and follow-up evaluations; and, "viral load guided care", where VLs are included with clinical and immunological evaluations. The protocol is approved by Kenya medical Research Institute (KEMRI-KEMRI SSC# 1717) and Walter Reed Army Institute of Research (WRAIR - WRAIR# 1591) Institutional review Boards (IRB)

A total of 820 adult patients initiating first line ART were recruited in the study. 410 participants were randomized to Arm A/Routine Care receiving MoH standard of care monitoring consisting of baseline CD4 and WHO staging every 6 months, or as clinically indicated, with CD4 and WHO staging criteria guiding care and treatment in addition to routine clinical evaluations. 410 patients were randomized to Arm B/Viral Load Guided care receiving MoH standard of care as in Routine Care/Arm A but also have VL monitoring at baseline and every 6 months, or as clinically indicated, to guide care and treatment.

Participants entering each Arm received Kenya MoH recommended standard of care, first and second-line ART as indicated [11.]

Primary objective of the study

1. To compare proportions of viral failures at 18 months of follow-up among adult patients initiating ART who are followed by either 1) routine CD4 and clinical care monitoring (Routine care/Arm A); or 2) routine VL, CD4 and clinical care monitoring (VL guided care/Arm B).
2. To evaluate the cost-effectiveness of routine VL monitoring in addition to CD4 and clinical monitoring in clinic-based ART management by measuring clinical and laboratory actual health outcome costs.

In line with the primary objective of the study are two primary endpoints

- Viral Failure
- Cost effectiveness

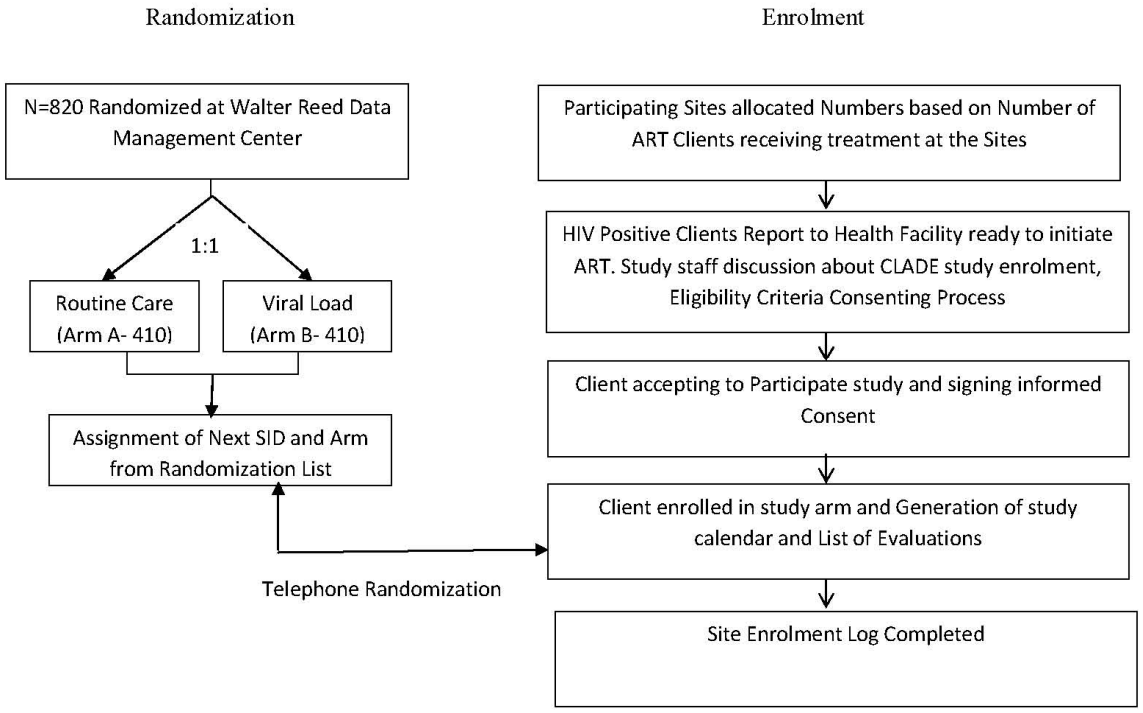
The study has a number of Secondary endpoints among them is **death/ Mortality** which is the basis of this project work.

Methodology

1. Randomization and Enrolment

Blocked Randomization scheme was used to generate (1:1) codes to either Routine Care (Arm A) or Viral Load Guided Care (Arm B) each participating site having 50% of patients enrolling being assigned to each Arm. The randomization codes were generated by the KEMRI/WRP CRC Information Technology (IT) Department and the list validated by the study statistician. The enrolment process started with participants signing informed consent followed by inclusion/exclusion criteria evaluation. The site coordinator at each site then called the KEMRI/WRP IT Department Manager or Assistant Manager for study Arm assignment. Both the randomization Arm and study ID (SID) were recorded on a randomization Log.

Figure 1 Randomization and Enrolment Flow Diagram



2. Study Area

This study analyzed data from the Kericho “CLADE” study, a prospective cohort study conducted in 7 district level, rural clinics (5 MoH, 2 Faith-based) staffed primarily by clinical officers and nurses, 820 treatment naïve patients were randomized to two treatment arms: CD4 guided Arm and Viral load guided Arm. The clinics are geographically spread across the south Rift valley province of Kenya.

3. Patient Clinic flow and visits

Enrolment of clients was done at the study sites with cell phone randomization between the rural clinic stations and the data management center in Kericho. All clients enrolled were given “calendars”, a clinic visit schedule showing when they were expected to turn up in the clinic for evaluations as per the protocol schedule of events. Clients were scheduled to turn up for clinic visits as per the table below:

Study Visit	Study Week	Weeks from Enrollment Date
1	Week 0	Enrolment date
2	Week 2	2 weeks
3	Week 4	4 weeks
4	Week 8	8 weeks
5	Week 12	12 weeks
6	Week 24	24 weeks
7	Week 36	36 weeks
8	Week 48	48 weeks
9	Week 60	60 weeks
10	Week 72	72 weeks

MOH standard of care monitoring consisting of baseline CD4 and WHO staging every 6 months, or as clinically indicated in addition to routine clinical evaluations. In addition participants in the viral load Arm received viral load evaluations every 6 months. Participants entering each Arm received Kenya MoH recommended standard of care, first and second-line ART as indicated [11.]

Data Collection and Management

Study case report forms were used to collect data from the study sites. The data on the CRFs were extracted from the patient clinic encounter forms by study coordinators (clinicians or Nurses) with a backup coordinator doing Quality Assurance. Data entry for the study was done on each study site by data clerks into a Microsoft SQL database with a username and password for both the front end and the backend. All the data collected were de-identified at respective sites before data entry and were only identified by unique study Identifiers. Data were then downloaded to a main database at the Kericho research station Data Management center. Data queries built into the SQL database to capture study endpoints and generate patient summaries.

Some components of Data analysis were done locally in Kericho through a mentorship program with validation of results by a US based statistical team that provided mentorship [12.]

The study sites for this study were in rural Kenya where eligibility criteria and enrolment was done. All the clinic visits, laboratory evaluations, CRF data extraction and data entry was also done at this clinics. Data download and generation of queries were done in the Kericho office and any correction was done on the CRFs at the sites with this being tracked back to the database. Data Management and analysis for this study was done at the Data management center (DMC) in Kericho with some statistical support from a team in the United States of America. Telephone randomization, data download and query resolution, data analysis and report generation activities were done at the Kericho DMC. The statistical center in the United States performed protocol specified Data analysis,

analysis validation for any data analysis done in Kericho. Some protocol reports generated by the US team as well as signing off on reports generated in Kericho.

For the purpose of this project data for the first 6 months in the study were downloaded and analyzed to determine the factors influencing early mortality of patients starting 1st line ART in rural Kenya.

Data Analysis

Student T-Test was used to compare baseline characteristics of continuous variables while Pearson chi-square analysis used to compare categorical variables. Log rank chi-square and Kaplan Meier Curves were used to compare mortality between arms. Logistic regression analysis was used to analyze predictors of mortality. All the analysis was done using STATA 10 software. A do file was created to be used for analysis along with the analysis data sets.

a) Descriptive data analysis

i. Baseline characteristics at study enrolment ; these are descriptive statistics tables showing baseline values compared between the two study arms

ii. Baseline characteristics by outcome; this section compares the baseline values for those with outcome (death) and those who were continuing the study at the time of analysis(6 months since starting ART)

b) Univariate data analysis

i. Dichotomizing and analysis of characteristics; this section converts continuous variables into common groups that would make clinical sense and breaks down proportions for each of the categories. These are then compared (Chi square analysis) for those participants with outcome and those continuing study follow up

ii. Kaplan Meier analysis; compares deaths between the two arms. Log rank chi square is used to show if there is any statistical difference

c) Multivariate data analysis

Logistic regression analysis; this is used to analyze predictors of mortality using Univariate and multivariate logistic models

1. Baseline Characteristics as at Study Enrolment

As shown in table 2.0 below age, cd4 count, viral load copies, body mass index were the same at baseline. There was no statistical difference between these characteristics when arm A and B were compared.

Table 2.0 Baseline Characteristics as at Study Enrolment

Characteristic	**Arm A (Routine Care)**		**Arm B (Viral Load)**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Age (Years)	37.5	9.0	37.8	9.1	0.69
CD4 (cells/mm^3)	164	109	168	104	0.56
Viral Load(copies/ml)	228,650	254,376.9	234,578	239,620.2	0.74
Body Mass Index (Kg/m^2)	21.0	4.3	21.3	3.8	0.18
Hemoglobin (g/dl)	11.2	2.5	11.3	2.4	0.68

2. Baseline Characteristics by outcome- continuous variables

As shown in table 2.1 below, gender and age were not significant baseline characteristics as analyzed by outcome, whereas cd4 count, viral load and BMI were significant characteristics by outcome.

Table 2.1 Baseline characteristics by outcome-continuous variables

		Participant Status		
Characteristics		Death at 24 Weeks on ART	Alive at 24 Weeks on ART	p value
Gender	N	56	762	0.142
	Male	29 (8.4%)	318 (91.6%)	
	Female	27 (5.7%)	444 (94.3%)	
Age (years)	Mean	37.7	37.6	0.95
	SD	8.9	9.0	
CD4 count (cells/mm^3)	Mean	95.4	171.2	< 0.01
	SD	95.5	105.4	

Table 2.1 Baseline characteristics by outcome -continuous variables continued

		Participant Status		
Characteristics		Death at 24 Weeks on ART	Alive at 24 Weeks on ART	p value
Viral Load (copies/ml)	Mean SD	382,489 283,631.5	221949 240497.9	< 0.01
Body Mass Index (kg/m^2)	Mean SD	18.9 3.6	21.2 4.0	< 0.01
hemoglobin (g/dl)	Mean SD	10.4 3.2	11.3 2.4	0.03

3. Chi-square Statistic- Categorical Variables by Outcome (Death)

Pearson Chi square analysis was used to show the difference in baseline characteristics per outcome- among death cases and those continuing the study.

Table 3.1 baseline characteristics by outcome (death)

Characteristic	**Category**	**Proportion died**	**p value**
Gender	Female	5.7 %	0.14
	Male	8.4 %	
WHO Stage	Stage 1 & 2	4.2 %	<0.0001
	Stage 3 & 4	13.7 %	
Age	>= 38 Years	7.2 %	0.74
	< 38 Years	6.6 %	
BMI	< 8g/dl	14.9%	<0.0001
	>= 8 g/dl	3.7 %	
CD4 count	< 50 cells/mm^3	16.1 %	<0.001
	>= 50 cells/mm^3	4.9 %	

Table 3.1 baseline characteristics by outcome (death) continued

Characteristic	**Category**	**Proportion death**	**p value**
Hemoglobin	< 18.5	20.7 %	0.002
	>=18.5	6.1 %	
Viral Load	< 100,000 copies/ml	3.3 %	0.004
	>= 100,000 copies/ml	8.5 %	

4. All Cause Mortality and Kaplan Meier Survival Curve

A total of 70 participants experienced mortality after 18 months study follow up. 56 of these occurring within the first 6 months as shown in table 4.1 below

a. Table 4.1 all Cause Mortality proportions in the study

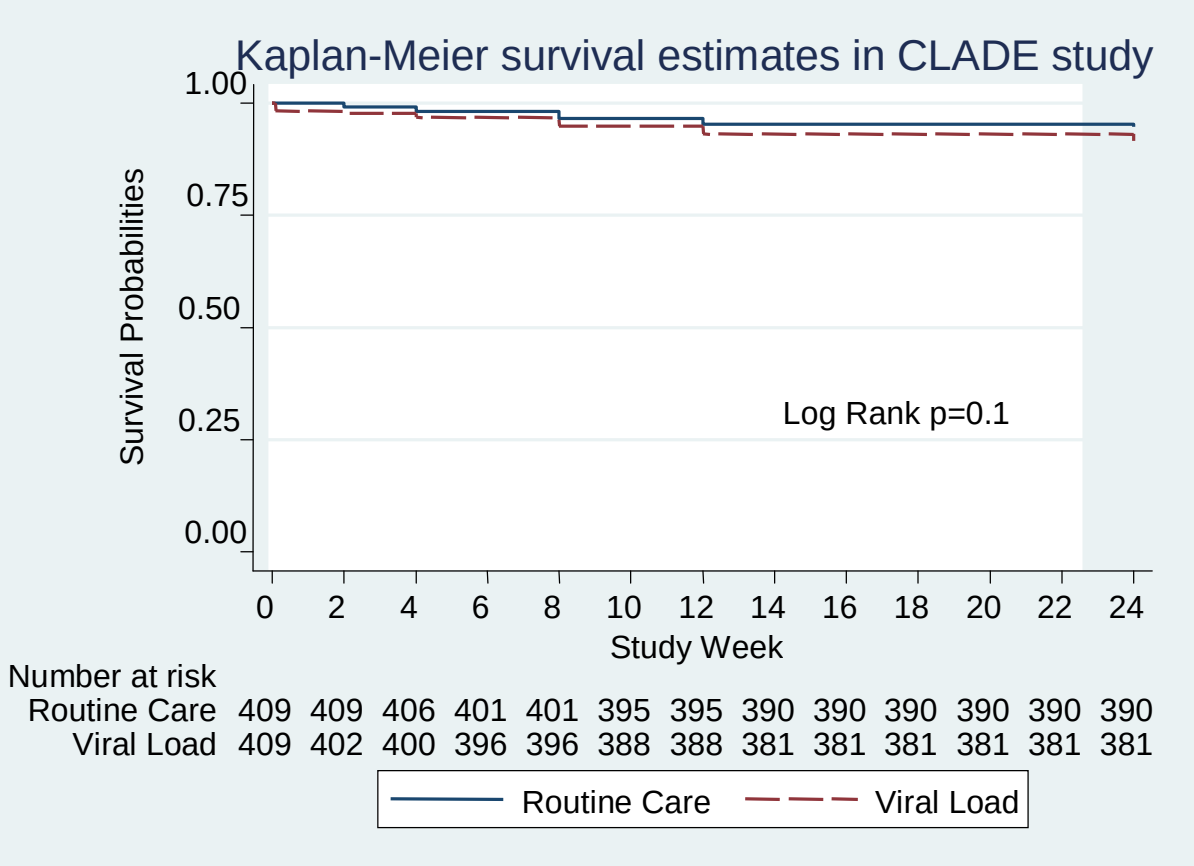
Time on ART	Freq.	Percent	Cum.
Before 6 Months	56	80	80
After 6 Months	14	20	100
Total	70	100	

b. Table 4.2 all Cause Mortality breakdown before 6 months in the study by Arm. This shows the proportions by Arm cases (deaths) and those continuing the study .

	Death		
Study Arm	No	Yes	Total
Routine Care (Arm A)	387 (94.6%)	22 (5.4%)	409
Viral Load (Arm B)	375 (91.7%)	34 (8.3%)	409
Total	762 (93.2%)	56 (6.8%)	818

p- value = 0.1

c. Figure 2. Kaplan-Meier Figure for All Cause Mortality



Note: All cause mortality survival curves were generated by the Kaplan-Meier method based upon data collected for 24 weeks (6 months) in the study for all participants. While collected as a secondary endpoint, the CLADE study is not designed or powered to draw Primary conclusions regarding mortality based upon Routine Care or Viral Load monitoring. The study sample size is calculated for the primary endpoint (18 month viral failure). Based upon the Kaplan-Meier analysis, the survival curves are not significantly different with a log rank p value= 0.10.

5. Predictors of Early Mortality

Logistic regression was used to analyze predictors of early mortality. This method was appropriate as the dependent variable (death) was a dichotomous variable with yes and no values. The logistic model relates the probability of success (*p*) with the explanatory variable (*X*) via the relationship as in the formula below

$$\log (p/1-p) = \alpha + \beta X$$

a) Univariate Logistic Regression of Predictors

Table 5.1

Characteristic	Category	Mortality		
		Relative Risk (RR)	**95% CI**	**p value**
Arm	A	Reference		
	B	1.6	0.916 - 2.778	0.1
Gender	Female	Reference		
	Male	1.5	0.871 - 2.583	0.14
Age	>=38	Reference		
	<38	0.9	0.463 - 1.744	0.75
CD4 (cells/m^3)	< 50	Reference		
	$\geq$ 50	0.26	0.15-0.47	<0.0001
VL (copies/ml)	< 100,000	Reference		
	$\geq$ 100,000	2.66	1.32- 5.32	0.006
WHO Stage	I or II	Reference		
	III or IV	3.66	2.10-6.37	<0.0001
BMI (kg/m^2)	< 18.5	Reference		
	$\geq$ 18.5	0.22	0.12-0.39	<0.0001
Hemoglobin (g/dl)	< 8.0	Reference		
	$\geq$ 8.0	0.24	0.09-0.64	0.005

Significant factors from the above Univariate logistic analysis (CD4 count, viral load, body mass index (BMI), Hemoglobin (Hgb) and WHO stage) were modeled in the multivariate analysis as shown in Table 5.2

b.) Multivariate analysis of the significant predictors

Table 5.2 Multivariate analysis of predictors

Characteristic	Categories	Mortality	
		RR (95% CI) – (p value) [1]	**RR (95% CI) – (p value) [2]**
CD4 (cells/m^3)	< 50	Reference	reference
	≥ 50	0.26 (0.15-0.47) – (<0.0001)	0.60 (0.24-1.51) – (0.286)
VL (copies/ml)	< 100,000	Reference	reference
	≥ 100,000	2.66 (1.32- 5.32) – (0.006)	1.36 (0.53-3.44) – (0.514)
WHO Stage	I or II	Reference	reference
	III or IV	3.66 (2.10-6.37) – (<0.0001)	2.43 (1.01-5.80) – (0.045)
BMI (kg/m^2)	< 18.5	Reference	Reference
	≥ 18.5	0.22 (0.12-0.39) – ((<0.0001)	0.44 (0.18-1.06) – (0.069)
Hgb (g/dl)	< 8.0	Reference	Reference
	≥ 8.0	0.24 (0.09-0.64) – (0.005)	0.25 (0.08-0.83) – (0.023)

1. Univariate model

2. Adjusted for CD4, VL, WHO Stage, BMI, and Hgb

The multivariate model shows WHO stage and hemoglobin (Hgb) as the significant factors controlling for CD4 count, viral load and body mass index (BMI)

Results

Descriptive

Of the 818, 70 (8.6%) died by the end of the study (18 months follow-up). 56 (80%) of the 70 deaths occurred early within 6 months of ART initiation while the other 20% died later as shown figure 3 below. There was no statistical significant difference for baseline characteristics (gender, cd4 count, viral load, body mass index, hemoglobin and age) as shown in table 2.1 and table 3.1

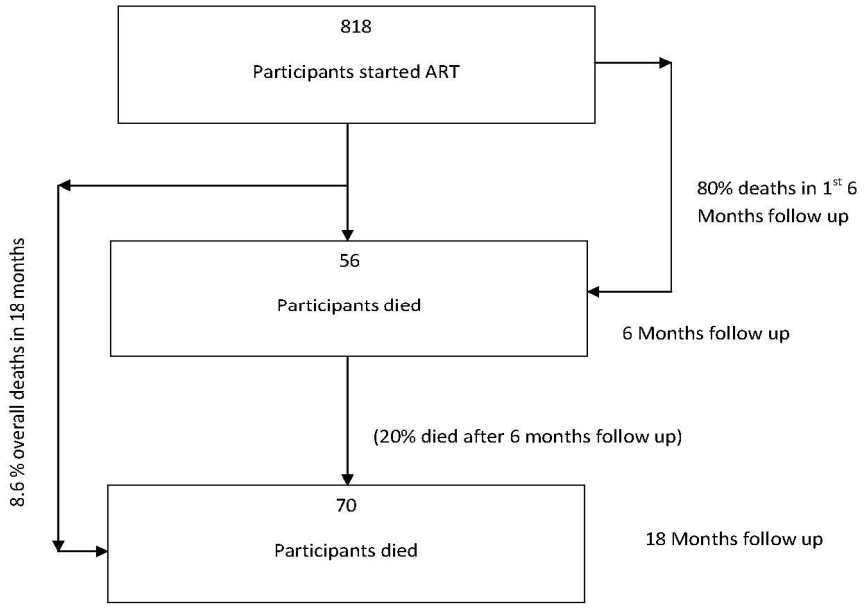
Univariate analysis of Predictors

In Univariate analysis Baseline viral load ($p < 0.006$), baseline Cd4 ($p<0.0001$), WHO stage III & IV ($p<0.0001$), Body mass Index ($p<0.0001$) and hemoglobin ($p<0.0001$) were independently predictive of death. (Table 5.1)

Multivariate analysis of Predictors

In the Multivariate analysis Hemoglobin ($p=0.02$) and WHO Stage 3 and 4 ($p=0.04$) are predictive factors controlling for BMI, Cd4 count and Viral load.

Figure3. Participant Mortality outcomes



Discussion

Participants enrolled into the CLADE study had similar baseline characteristics between the two study arms. High mortality was noted in the first 6 months of the study with 80% of the cases dying compared to 20% that experienced mortality at the last 6 months of the study. This presents very important information for policy makers who are concerned with treatment of HIV patients and initiation of ART. Early diagnosis of disease and initiation of ART is key to reducing early mortality.

As shown in table 2.1 clients who experienced mortality within 6 months of ART initiation were enrolled in the study with low baseline CD4 count (mean 95.4 cells /$mm^{3)}$. This suppressed immunity could have been a contributing factor to early mortality informing that clients need to be initiated ART early enough when their CD4 is still high. In the Univariate analysis of predictors BMI was shown to be a significant factor predictive of Mortality. This is consistent with results of a study conducted on patients with advanced HIV initiating antiretroviral therapy in the South Rift Valley where it was found that initiating underweight patients had a 2.7-3.0 times increased risk of hospitalization and mortality compared to those who were not underweight [13.] A study in Ethiopia also showed weight loss as a problem in patients treated with HAART, and its presence should alert further search for underlying causes. [14.] Our study showed low hemoglobin levels were predictive of mortality and remain a big challenge in the treatment of HIV patients in the region. A similar study in Tanzania showed that mortality increased with decreasing Hemoglobin [15.] Opportunities exist for more targeted studies to understand this factor as it was shown to be highly significant statistically in predicting mortality.

Conclusion

In this study we have shown that patients who start ART treatment with low CD4 count, high viral load, low hemoglobin and low BMI were more likely to experience early mortality. Low mortality rates can be achieved in patients starting ART in rural clinics of Kenya. Aggressive HIV testing programs need to be strengthened for early detection of infection, CD4 count evaluation for these identified patients and viral load where available will help in recruiting them to treatment programs early enough. Malnutrition and anemia require intervention to improve survival of HIV positive Clients.

Recommendation

The results of this study show hemoglobin as a significant factor predictive of early mortality of HIV Patients starting ART in rural Kenya. We recommend that more studies are done to understand the causes of low hemoglobin levels and provide a way forward in tackling the problem in resource limited settings. Interventions to address this problem need to be put in place as part of comprehensive HIV treatment package for those already infected and are starting/ on treatment.

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