

THE PREDICTIVE VALUE OF ANAEMIA IN DETERMINING MORTALITY IN
PATIENTS WITH HIV AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA,
ZAMBIA.

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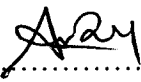
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DECLARATION

I, Dr LISULO WIMBITA..... hereby certify that this dissertation is the product of my own work, and in submitting it for my Master of Medicine in Internal Medicine degree, further attest that it has not been previously submitted either wholly or in part for any other degree at this or any other university.

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CERTIFICATE OF APPROVAL

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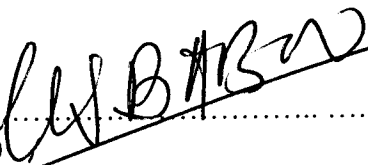
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CERTIFICATION OF COMPLETION

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ABSTRACT

Objective: The aim of the study was to determine the predictive values of anaemia (lower levels of hemoglobin), CD4 count and WHO clinical staging in determining mortality among HIV positive patients enrolling on the ART programme.

Design/ Setting: It was a diagnostic study conducted over six months at the UTH Department of Medicine. A total of 340 patients that enrolled on the GRZ ARVs scheme at UTH were recruited. Of these 170 were deceased and 170 were living. Diagnostic parameters of the initial CD4 count, haemoglobin and WHO clinical staging were done on all the patients who participated in the study. The information collected was entered onto the questionnaires for analysis.

Results: The majority of patients were between the age group of 31 – 40 years (42.9%), with more females (56.8%) than males. A large number of patients 82.9% were anemic. In predicting mortality, CD4 count had the highest sensitivity of 94.1%. WHO clinical staging had a sensitivity of 77.7 %, and haemoglobin had a sensitivity of 68.2%. Combined haemoglobin, CD4 count and WHO clinical staging had relatively lower sensitivities between the ranges of 52.4% and 65.9%

Conclusion: Most of the patients enrolling for ART were anaemic. WHO clinical staging, CD4 count and haemoglobin levels are good predictors of mortality and therefore can be used to identify patients at high risk.

Recommendations: All patients with HIV enrolling for the ART program should be screened for anaemia. Haemoglobin levels and WHO clinical staging can be used to identify patients at highest risk of mortality in resource limited areas where CD4 counts and viral loads are not available.

DEDICATION

To mum and dad for teaching me to love and to respect life.

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First and foremost I want to thank the Almighty God for the countless and priceless blessings, without which this work would not have been possible.

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LIST OF ABBREVIATIONS

WHO	World Health Organisation
CDC	Center for Disease Control
HIV	Human Immunodeficiency Virus
FBC	Full Blood Count
ESR	Erythrocyte Sedimentation Rate
U/E	Urea and electrolytes
UTH	University Teaching Hospital.
Hb	Haemoglobin
ART	Antiretroviral Treatment
HAART	Highly Active Antiretroviral Therapy
AIDS	Acquired Immunodeficiency Syndrome
CD4	Cluster Differentiation type 4 (type of lymphocyte)
PPV	Positive Predictive Value
NPV	Negative Predictive Value
CI	Confidence Interval
ARVs	Antiretrovirals
CSO	Central Statistics Office
STIs	Sexually Transmitted Infections
2,3 DPG	2,3 Diphosphoglycerate
LCMS	Living Conditions Monitoring Survey
PCV	Packed Cell Volume
TB	Tuberculosis
MAC	Mycobacterium Avium Complex
MSM	Men having Sex with Men
CMV	Cytomegalovirus
PPV	Positive Predictive Value
NPV	Negative Predictive Value

INTRODUCTION

Zambia is a land locked country covering an area of 752,612 square kilometers. The 2000 national census reported a total population of 10.3 million, with a growth rate of 2.9 percent per annum as at 2000. Zambia's population is essentially of young people. Approximately 67% comprises children aged 15 years or younger (Central Statistical Office, 2004, 2003).

Zambia is among the three most highly urbanised countries in Africa, along with Algeria and South Africa. Four out of ten Zambians live in the urban areas, most of which are located along the line of rail, where the social amenities such as housing, sanitation have been considerably overstretched. The countries poor economic performance has resulted in high poverty levels. Currently, according to the CSO LCMS 2004, around 73% of Zambians are classified as poor with poverty being more prevalent in rural areas than urban areas (83% and 56%, respectively). This therefore means that the majority of Zambia's population dwells in low sociogeolocations. Of these, the majority squatter in the peri urban areas of major towns. The educational level of these people is very poor and often exposed to the outbreaks of many communicable diseases such as cholera; infectious diseases such as tuberculosis, sexually transmitted infections and HIV. Fifteen years of unpublished data from the department of community medicine have shown the average income of this group to be between K150, 000 – K300, 000 per month, with poor calorie intake exhibiting low nutritional status. Anaemia in such a population is a common phenomenon and with any infectious disease, it is likely to cause an infectious cycle

For this reason Zambia's demographic and socioeconomic situation is conducive to the spread of communicable diseases such as sexually transmissible infections and HIV (Matondo P, 1993). The first case of AIDS was diagnosed in Zambia in 1984 and currently 16% of Zambians in the age group of 15- 49 years are HIV positive,

with the prevalence being more than twice as high in urban areas as in rural areas (23% and 11%, respectively) (Central Statistical Office, 2004).

The high levels of poverty with the resultant lower standards of living lead to poor nutrition. This contributes to anaemia which will result from a variety of causes such as malaria, HIV infection, worm infestations, tuberculosis (Alan F F, 2004, Alan F F et al., 2003, Gilles HM, 1981, Horsburgh CR, 1991, Saag MS, 1997, Biemba G et al., 2000). On average 600- 700 patients per year are admitted with anaemia at UTH (University Teaching Hospital Lusaka, 2005), though the actual incidence and prevalence of anaemia is not known. The University Teaching Hospital, where the study was undertaken, is the largest and main referral hospital in Zambia. It acts as a specialist and referral hospital for all hospitals in the country. It has a 1800 bed capacity, of which 300 are in the Department of Medicine. The government of Zambia largely funds the hospital. Usually there are more than 1800 patients admitted per day due to the high disease burden arising mainly from the high HIV/AIDS burden.

Anaemia becomes increasingly frequent as HIV disease progresses, and has been found in 63%-95% of those with HIV infection at some point during the course of their disease. There is an increased incidence of anaemia with advanced clinical stages of HIV disease. Three percent of those with HIV infection alone develop anemia at 1 year of follow up, compared with 12% of those with immunological AIDS (CD4 count less than 200 cells/ μ L) and 37% of those with clinical AIDS (Mildvan D, 2003, Sullivan PS et al., 1998).

There is a wide range of etiological factors that may cause anaemia in HIV. This will range from anaemia of chronic disease to anaemia induced by drugs used in treating HIV, autoimmune hemolysis, nutritional deficiencies such as vitamin B12 or folate. The others are: malignancies associated with HIV such as Kaposi's sarcoma, opportunistic infections such as tuberculosis and pre-existing conditions such as

sickle cell disease(Ashlee M et al., 1998, Paul V A et al., 2003, Volberding PA et al, 2004, Elliot AM et al., 1995).

The anaemia contributes to high morbidity and mortality in this condition. However treatment of anaemia in HIV infection has been associated with improved survival (Paul V A et al., 2003, Sullivan PS et al., 1998).Therefore understanding the association between anaemia and survival in HIV infected persons is important because treatments for anaemia are readily available. They include blood transfusion, recombinant human erythropoietin, and, in drug induced anaemia, cessation of such drugs (Spivak JL et al., 1989, Saag MS, 1997).

Since anaemia is common in HIV infection, it would be of clinical relevance to evaluate the levels of anemia in Zambian HIV patients. It would also be important to establish which levels of haemoglobin are associated with the shortest survival. This study therefore will look at the prognostic values of hemoglobin in relation to other markers used in the care of HIV patients such as CD4 and WHO clinical staging and compare their ability to predict mortality in HIV patients. This is important and of clinical relevance in the sense that the findings will be used to maximise the care of HIV patients with anaemia so as to improve their quality of life and prevent death.

LITERATURE REVIEW

Anaemia is defined as a reduction of the haemoglobin concentration, red cell count, or packed cell volume (PCV) below the normal ranges for age, sex and pregnancy state (Ledingham JCG et al., 2000).

The World Health Organization recommends that anaemia should be considered to exist in adults whose hemoglobin levels are lower than 13 g/dl (males) or 12 g/dl (females). However, these guidelines are rather arbitrary as there are many apparently normal individuals whose haemoglobin concentration is below their optimal levels due to various genetic and common environmental factors that can affect the reference ranges (Alan F F et al., 2003, Ledingham JCG et al., 2000).

Anaemia is a major world health problem, especially in developing countries (e.g. Zambia). In general, anaemia is common in women between the ages of 15 and 44 years and thereafter becomes relatively less frequent. The prevalence increases again in the 75 and over age group. It is only in the later group that the prevalence in males and females is almost the same (Ledingham JCG et al., 2000).

The function of the red blood cells is to carry oxygen between the lungs and the tissues, though tissue oxygenation is a result of a series of complex interactions of different organ systems. Anaemia therefore reduces the oxygen carrying capacity of the blood, resulting in widespread organ dysfunction and an extremely varied clinical picture. This picture is dependent on whether the anaemia is of rapid or insidious onset. Most manifestations of any given anaemia are common to all anaemias. Their intensity is determined by the rate of onset, the extent to which the haemoglobin concentrations are lowered, the degree of reduction in blood volume, and the adequacy of cardiopulmonary compensation. Anaemia of abrupt onset is far more dangerous than insidious anaemia of comparative severity.

Anaemia results from three basic mechanisms. These mechanisms are blood loss (acute or chronic), decreased production of red cells and increased destruction of

red cells (hemolysis). Blood loss can be due to hookworm infestations, peptic ulcers, heavy menses and epistaxis. Decreased production of red blood cells is due to a lot of factors some of which are poor nutrition with subsequent deficiencies of vitamin B12 and folate, chronic infections such as tuberculosis and HIV, malignancy usually lead to anaemia of chronic disease. Increased destruction of red blood cells occurs in inherited disorders of red blood cells such as thallasaemias, sickle cell disease and glucose-6 phosphate dehydrogenase deficiency (Alan F F, 2004, Dacie JV and Lewis SM, 1991, Gilles HM, 1981).

Despite the different mechanisms through which anaemia is caused, the body's compensatory mechanisms are the same. These involve increasing the release of oxygen from haemoglobin to the tissues through increased levels of 2, 3 DPG: increased cardiac output, heart rate and stroke volume; enhancing blood flow to vital organs/tissues with high oxygen requirements while reducing the flow to other organs such as the skin and kidneys. These mechanisms lead to the symptoms of anaemia such as pallor, thumping palpitations, dizziness, postural faintness or syncope, poor concentration, irritability and tinnitus. Furthermore breathlessness, visual disturbances and tachypnoea are usually signs of advanced hypoxemia.

The pathophysiology of anaemia can therefore be considered under the following stages: compensated anaemia, decompensated anaemia and anaemic heart failure. Compensated anaemia is associated with mild to moderate anaemia in which there is an increase of 2, 3-DPG concentration in red blood cells. This leads to the shifting of the oxygen dissociation curve of haemoglobin to the right (decreased oxygen affinity), and increased oxygen release to tissues by up to 40%. In this condition there is an increase in stroke volume at rest and becomes exaggerated with a tachycardia on exertion. Vasodilatation increases blood flow to organs such as myocardium and brain. Vasoconstriction to the skin and kidneys result in reduction of blood flow to these organs. Patients complain of breathlessness on exertion only and may only have pallor on examination except for the symptoms

and signs of the underlying cause of anaemia (Alan F F, 2004, Ledingham JCG et al., 2000, Bellingham AJ, 1974).

Decompensated anaemia is found in patients whose haemoglobin falls below 7g/dl. The major mechanism for improving oxygen delivery is by increasing the cardiac output. Both stroke volume and the heart rate are raised at rest. Ventricular workload is reduced by the low viscosity of blood and by peripheral vasodilatation; circulation time is short and blood volume is reduced in about 25% of patient. Patients are breathless at rest with tachycardia, arterial and capillary pulsations with wide pulse pressure and haemic ejection systolic murmurs (Dacie JV and Lewis SM, 1991).

Anaemic heart failure happens when the haemoglobin falls approximately below 3g/dl. In this case there is insufficient oxygen supply to the myocardium: no further increase in cardiac output is possible and a high output cardiac failure develops with an expansion of the plasma volume. Patients are severely breathless and may complain of angina, claudication and fatigue. Patients have cardiomegaly, jugular vein engorgement, pulmonary edema, hepatomegally peripheral edema and sometimes ascites (Alan F F, 2004, Dacie JV and Lewis SM, 1991).

Through the above pathophysiological processes anaemia has been known to complicate many infections such as malaria, tuberculosis, liver diseases, renal diseases and many degenerative disorders leading to repeated admissions and poorer outcomes if not corrected. Mostly the anaemia associated with these disorders is anaemia of chronic disease, which is the second most common type of anaemia after iron deficiency anaemia, though the latter is invariably found in these diseases. Invariably the human immunodeficiency virus by virtue of it being a chronic infection also leads to anaemia of chronic disease.

Anemia of chronic disease is immune driven through cytokines and the cells of the reticuloendothelial system, leading to changes in iron homeostasis, the proliferation

of erythroid progenitor cells, the production of erythropoietin, and the lifespan of red cells, all of which contribute to the pathogenesis of the anaemia. Also the disease underlying this anaemia does contribute to the disturbance in the process of erythropoiesis (Horsburgh CR, 1991, Saag MS, 1997).

Extensive spread of HIV-1 began in the late 1970s and early 1980s, and was just isolated in 1983 with the affected populations being men who have sex with men (MSM) in some urban areas of the Americas, Australia and Western Europe, and men and women with multiple sexual partners in East and Central Africa. HIV-2 was isolated during the 1980s and, until recently, has been confirmed to West Africa (UNAIDS, 2004, Royce RA et al., 1997)

Sub-Saharan Africa is the worst affected region, having around 70% of the global total of HIV-positive people. By the end of 2000, 34.7 million adults and 1.4 million children were living with HIV worldwide. Around 80% of deaths from AIDS in 2000 occurred in Sub-Saharan Africa (UNAIDS, 2004).

The presence of anaemia in an HIV positive person is significantly associated with quick progression to AIDS and increased risk of death. Consequently, recovery from anaemia is associated with a decreased risk of death (Sullivan PS, 2002, Volberding P, 2002)

There is a wide range of etiological factors that may cause anaemia in HIV disease and these can be broadly divided into two categories: -

Decreased Production

- Drugs: Zidovudine, Septrin, Amphotericin B, Ganciclovir, Dapsone, Delavirdine.
- Deficiencies: Erythropoietin, Iron, Folate, Vitamin B12
- Infections: HIV, Parvovirus B19, Mycobacterium Avium Complex (MAC), tuberculosis, histoplasma.

- Neoplasia: Non Hodgkin's Lymphoma, multiple myeloma, Cattleman's disease, Hodgkin's disease.
- Miscellaneous: Anaemia of chronic disease, pre-existing condition e.g. sickle cell disease.

Increased Loss

- Haemolysis: Thrombocytopenic purpura, Glucose-6-Phosphate dehydrogenase deficiency, autoimmune hemolytic anaemia.
- Idiopathic
- Drugs: (Ceftriaxone, indinavir)
- Infections: (CMV = Cytomegalovirus)
- Gastrointestinal bleeding: Kaposi's sarcoma, Non-Hodgkin's lymphoma, infection (CMV, Candida).
- Hypersplenism: Infection, Lymphoma, Hemophagocytosis, Cirrhosis (hepatitis B virus, hepatitis C virus)(Ellaurie M et al., 1990, Sullivan PS et al., 1998, Keisu M et al., 1990)

Despite the various etiological causes of anaemia in HIV disease, the anaemia associated with it is anaemia of chronic disease (Levine AM, 2003). Therefore understanding the association between anaemia and survival in HIV infected persons is important because treatments for anaemia are readily available. These include blood transfusion, recombinant human erythropoietin, and, in drug induced anaemia, cessation of such drugs.

Since most of HIV infected persons become anaemic through various processes during the course of the infection it would be important to establish the role anaemia plays in predicting mortality in comparison with the other makers of disease progression such as CD4 count and viral load since both the CD4 and viral load measurements have widely been regarded to be the essential optimum in the management of HIV infection. The CD4 cell count has been shown, in numerous clinical trials and natural history studies, to be an independent risk factor for progression to AIDS and death. However it has two major limitations; it is subject

to considerable variations e.g. interassay variations, changes due to intercurrent illnesses and diurnal variation. In this respect the CD4 cell count is therefore not ideal for predicting future immunological damage in any given individual (Hughes MD et al, 1997, Metcalf JA et al., 1997).

The other parameter used in the monitoring of patients with HIV is the WHO clinical staging. This staging system was developed and published in 1990. It includes 32 clinical conditions and three CD4 cell count levels. Stages 1 and 2 are the earliest stages in HIV disease, with stages 3 and 4 being the late stages of HIV. Stage 4 is the AIDS clinical stage. This clinical staging system is widely used in managing patients with HIV (WHO/UNAIDS 1998).

The other parameters directly related to the cause rather than the consequence of immunological damage is the HIV RNA levels (viral load). The viral load level is a more powerful predictor of the future rate of disease progression than the CD4 cell count, particularly in early stage infection (Hughes MD et al, 1997, Kuritzkes DR, 1999). It is now a known factor that HIV infection and anaemia go parallel with each other. High viral loads and low CD4 cell counts are a common finding in such populations. Therefore, early detection of anemia could be identified as a marker in such situations.

PROBLEM STATEMENT

The majority of HIV patients attending the University Teaching Hospital and many other Zambian hospitals and clinics are anaemic. Despite the relative frequency of anaemia in this group of patients, information concerning anaemia is still poor. Currently there are no Zambian studies done to assess and evaluate the predictive value of haemoglobin in predicting mortality in HIV patients. This study will assess which level of haemoglobin is associated with the shortest survival. The study will also assess the sensitivity and specificity of haemoglobin in predicting the outcome of patients suffering from HIV disease.

STUDY JUSTIFICATION

Anaemia is a common complication among patients with HIV disease and can be found in approximately 63-95% of those with HIV infection during the course of the infection at some point (Sullivan PS et al., 1998). Despite the relative frequency of anaemia and the heavy burden of many patients with HIV infection attending the University Teaching Hospital, information on anaemia is very poor and there are no studies done yet to assess the role anaemia plays in predicting mortality in these patients.

This study therefore was important in establishing the levels of anaemia among HIV patients being attended to at UTH. It also established the correlation between the level of haemoglobin, WHO clinical staging and CD4 count and the specificity and sensitivity of haemoglobin level in predicting the clinical outcome of patients infected with HIV.

Since the presence of anaemia in an HIV infected patient is significantly associated with an increased risk of death, conversely, recovery from anaemia is associated with a decreased risk of death. However the predictive values of hemoglobin in determining mortality had not been investigated. Therefore, it was important to establish which levels of hemoglobin are greatly associated with death so as to aggressively treat the anaemia in such patients and reduce the risk of death.

RESEARCH QUESTION

Can anaemia, CD4 count and WHO HIV clinical staging be used to predict mortality among patients with HIV enrolling for the ART programme at UTH?

HYPOTHESIS

The presence of anaemia alone despite the cause is associated with a significant increase in morbidity and mortality in HIV infected patients.

AIMS AND OBJECTIVES OF THE STUDY

AIM: To determine the prognostic value of anaemia, CD4 cell count and WHO clinical staging in predicting mortality in a cohort of patients enrolling on the ART programme.

Specific objectives:

1. To determine the predictive values for Hb in determining mortality in HIV patients
2. To determine the prognostic value of CD4 cell count in determining mortality in HIV patients.
3. To determine the predictive values for WHO clinical staging in determining mortality in HIV patients.
4. To determine the agreement between Hb and WHO clinical staging in determining mortality in HIV patients.
5. To determine the agreement between Hb and CD4 in determining mortality in HIV patients.
6. To determine the joint predictive values of Hb, CD4 count, WHO clinical staging in determining mortality among HIV patients.

ETHICAL CONSIDERATION

Permission to carry out a study involving human subjects was sought from the Research Ethics Committee of the University of Zambia. The study subjects were required to give an informed consent to freely participate in this study and they reserved the right to withdraw from the study at any given point. As for the deceased patients, permission was gotten from the executive director of UTH to have access and extract information from their medical records. Patient's information was treated with the highest confidentiality and the information volunteered was used solely for the purposes of the study. Necessary clarification and care was provided to the study participants at all times during the study period.

METHODOLOGY

STUDY SETTING:

The study was carried out from August – December 2005 in the department of medicine of the University Teaching Hospital, Lusaka .The UTH is the largest hospital in Zambia with a bed capacity of 1,800 and serves as the main referral centre for all the patients in the country and the 23 clinics in Lusaka district.

The Department of Medicine comprises the medical admission ward, E-block medical wards and clinic 5 (medical clinic).It has a 300 bed capacity and all the patients with medical problems are referred to the department. Currently the Department of Medicine runs an ART programme of which there are over 4,000 patients on the programme and the records are still being updated.

STUDY DESIGN

This was a diagnostic study and for all the analyses anaemia was defined as a haemoglobin concentration of less than 12g/dL.

The patient hospital number was picked using systemic random sampling of 1 in 5 from the database in the Department of Medicine-clinic 5 without prior knowledge of the levels of Hb and other clinical data. Using the final outcomes of death and alive, 170 subjects were picked among the deceased and 170 among the living in the database of patients prior to being treated for HIV infection and receiving antiretroviral treatment at UTH.

Structured questionnaires were used to collect data from the deceased patient's files whilst for living patients, the same questionnaires were administered after getting the permission to do so. The laboratory data of the initial Hb, CD4 count and WHO clinical staging was recorded from the deceased patient's files whilst blood for Hb and CD4 was collected and a clinical examination was done to ascertain the WHO

HIV clinical staging on the living patients. The results were recorded in the questionnaires.

SAMPLE SIZE

The study sample size of 340 patients i.e 170 deceased and 170 alive was aimed at considering a specificity of 85%, sensitivity of 90% and a 95% confidence level using EpiInfo version 6 statcalc. This was based on the total number of 900 patients entered in the computerised UTH ARVs data base at the time of writing the proposal (at 85% specificity sample size was 161, and with 90% sensitivity, the sample size was 120). From inception of the ARVs programme more than 4000 patients have been enrolled and the data base is still being updated. The same larger sample size of 161 was used in considering an efficient study with equal sample sizes for the dead and alive. A round up figure of 170 was used.

Inclusion Criteria:

- Patients with HIV disease seen and attended to in the Medical Department (Ph. V medical admission ward, E-block medical wards, Clinic 5- medical clinic) were recruited in this study.
- Age 16-60 years
- Patients on the ARVs programme who consented to be included on the study

Exclusion Criteria

- Age less than 16 years or above 60 years
- Refusal of consent to be included in the study.
- Pregnancy

DATA COLLECTION

An interviewer - administered questionnaire was used to collect information from the patients after consent was given. The findings of the physical examination and laboratory tests were entered onto the questionnaires using the study numbers that were allocated to each patient. Data collection took six months, from August to December 2005. Six medical students were recruited as research assistants, and the physical examination findings and the WHO HIV clinical staging were counter checked on each patient by the researcher. As for the deceased, the data was collected from the files and entered on the questionnaires.

DATA ANALYSIS

After collection, the data from the questionnaires and results from the laboratory were entered into the computer and were analyzed using SPSS software with confidence intervals set at 95%.

In order to determine the prognostic values of Hb, CD4 count, WHO clinical staging, diagnostic parameters of specificity, sensitivity, test the efficiency and negative and positive predictive values were computed for each of the various factors or a combination of more than one factor under investigation.

Sensitivity is defined as the ability of the test to correctly identify the true positives while specificity is the ability of the test to correctly identify the true negatives. The sensitivity and specificity of a test are calculated using the following formula i.e. a 2x2 table

TABLE 1: A 2x2 table for calculating sensitivity and specificity.

	Dead	Alive	Total
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b+ c + d

Therefore,

$$\text{Sensitivity} = \frac{a}{a + c}$$

$$\text{Specificity} = \frac{d}{b + d}$$

The Positive Predictive Value is the probability of a patient with a positive test being truly positive and is dependent on the prevalence of the condition under investigation and the sensitivity. Similarly, the Negative Predictive Value of a test is the probability that the patient with a negative test being truly negative and is also dependent on the prevalence and specificity.

The mortality rate due to HIV at UTH, from UTH records was 21% and this was used to calculate the positive and negative predictive values.

$$\text{PPV} = \frac{\text{Prevalence} \times \text{Sensitivity}}{\text{Prevalence} \times \text{Sensitivity} + (1 - \text{Specificity}) \times (1 - \text{Prevalence})}$$

$$\text{NPV} = \frac{\text{Specificity} \times (1 - \text{Prevalence})}{(1 - \text{Sensitivity}) \times \text{Prevalence} + \text{Specificity} \times (1 - \text{Prevalence})}$$

RESULTS

A total of 340 patients were included in the study, 170 were deceased and 170 were alive.

SAMPLE DESCRIPTION

TABLE 2: Age Distribution.

	n	(%)
Below 21	7	(2.1)
21 – 30	57	(16.8)
31 – 40	146	(42.9)
41 – 50	96	(28.2)
Above 50	34	(10.0)
Total	340	(100.0)

The majority of patients were below 50 years, with the highest number in the age group between 31 and 40 years.

TABLE 3: Sex Distribution

	n	(%)
Male	147	(43.2)
Female	193	(56.8)
Total	340	(100.0)

There were more females (56.8%) than men in the study.

TABLE 4: Marital Status

	n	(%)
Single	52	(15.3)
Married	178	(52.4)
Divorced	30	(8.8)
Widowed	80	(23.5)
Total	340	(100.0)

The majority of the participants were married (52%) followed by the widows (23.5%) and the least were the singles

TABLE 5: Education Status

	n	(%)
None	48	(14.1)
Primary School	60	(17.6)
Secondary School	109	(32.1)
Tertiary	123	(36.2)
Total	340	(100.0)

The majority of the patients had a minimum of primary school education (85.9%) with only (14.1%) having not had any formal education.

TABLE 6: Occupation

	n	(%)
Employed	205	(60.3)
Not Employed	135	(39.7)
Total	340	(100.0)

The majority of the patients (60.3%) were employed

TABLE 7: Hemoglobin levels

	n	(%)
1 – 3	10	(2.9)
4 – 6	55	(16.2)
7 – 9	99	(29.1)
10 - 12	118	(34.7)
>12	58	(17.1)
Total	340	(100.0)

Most of the patients included in the study (n = 282, 82.9%) were anemic with the majority of patients having hemoglobin levels between 10 – 12 g/dl.

TABLE 8: Hemoglobin level as a diagnostic test

HB (g/dl)	DEAD	ALIVE
HB ≤ 9	116	48
HB > 9	54	122
Prevalence		21.0%
Sensitivity		68.2% (61.2 – 75.2 %)
Specificity		71.8% (65.0 – 78.5%)
Positive Predictive Value		39.1%
Negative Predictive Value		89.5%
Test Efficiency		70.0 % (65.1 – 74.9 %)

Table 7 above shows the levels of diagnostic parameter of anemia which has a sensitivity of 68.2%, specificity of 71.8% and a positive predictive value of 39.1%

TABLE 9: WHO Stage 1 as a prognostic test

WHOStage 1	DEAD	ALIVE
Yes	0	7
No	170	163
		9
Prevalence		21.0%
Sensitivity		0.0 % (0.0 – 0.0 %)
Specificity		95.9 % (92.9 – 98.9 %)
Positive Predictive Value		0.0%
Negative Predictive Value		78.3 %
Test Efficiency		47.9 % (42.6 – 53.3 %)

Table 8 above shows specificity of 95.9% and the negative predictive value is 78.3%. However, the sensitivity is shown to be zero as it could not be calculated for this variable because of the empty cell with zero number of patients that died in WHO stage 1.

TABLE 10: WHO stage 2 as a prognostic test

WHO stage 2	DEAD	ALIVE
Yes	1	17
No	169	153
Prevalence	21.0 %	
Sensitivity	0.6 % (- 0.6 – 1.7 %)	
Specificity	90.0 % (85.5 – 94.5 %)	
Positive Predictive Value	1.5 %	
Negative Predictive Value	77.3 %	
Test Efficiency	45.3 % (40.0 – 50.6 %)	

The specificity of WHO stage 2 was high at 90.0% with the negative predictive value of 77.3%. The sensitivity was very low at 0.6% and the positive predictive value was 1.5%.

TABLE 11: WHO stage 3 as a prognostic test

WHO stage 3	DEAD	ALIVE
YES	37	77
NO	133	93
Prevalence		21.0 %
Sensitivity		21.8 % (15.6 – 28.0 %)
Specificity		54.7 % (47.2 – 62.2 %)
Positive Predictive Value		11.3 %
Negative Predictive Value		72.5 %
Test Efficiency		38.2 % (33.1 – 43.4 %)

Table 10 above shows that at WHO stage 3, the sensitivity was 21.8% and specificity of 54.7%. The positive predictive value was only 11.3% as compared to the negative predictive value of 72.5%.

TABLE 12: WHO Stage 4 as a prognostic test

WHO Stage 4	DEAD	ALIVE
YES	132	69
NO	38	101
Prevalence	21.0 %	
Sensitivity	77.6 % (71.4 – 83.9 %)	
Specificity	59.4 % (52.0 – 66.8 %)	
Positive Predictive Value	33.2 %	
Negative Predictive Value	90.9 %	
Test Efficiency	68.5 % (63.6 -73.5 %)	

WHO stage 4 had sensitivity of 77.6%, specificity of 59.4% and positive predictive value of 33.2% and a negative predictive value of 90.9%

TABLE 13: Combined WHO Stages 1&2, 3&4 as prognostic tests

WHO Stage	DEAD	ALIVE
3 & 4	169	146
1 & 2	1	24
Prevalence	21.0 %	
Sensitivity	99.4 % (98.3 – 100.6 %)	
Specificity	14.1 % (8.9 – 19.4 %)	
Positive Predictive Value	23.5 %	
Negative Predictive Value	98.9 %	
Test Efficiency	56.8 % (51.5 – 62.0 %)	

The sensitivity for combined WHO stages 1 & 2; 3 & 4 was 99.4% with specificity of 14.1%. The positive predictive value was only 23.5%

TABLE 14: CD4 ≤50 as a prognostic test

CD4	DEAD	ALIVE
≤ 50	72	38
> 50	98	132
Prevalence	21.0 %	
Sensitivity	42.4 % (34.9 – 49.8 %)	
Specificity	77.6 % (71.4 – 83.9 %)	
Positive Predictive Value	33.5 %	
Negative Predictive value	83.5 %	
Test Efficiency	60.0 % (54.8 – 65.2 %)	

The sensitivity for CD4 50 was 42.4%, specificity 77.6% and a high negative predictive value of 83.5%. The positive predictive value was 33.5%

TABLE 15: CD4 ≤ 100 as a prognostic test

CD4	DEAD	ALIVE
≤100	121	68
>100	49	102
Prevalence		21.0 %
Sensitivity		71.2 % (64.4 – 78.0 %)
Specificity		60.0 % (52.6 – 67.4 %)
Positive Predictive Value		32.1 %
Negative Predictive Value		88.7 %
Test Efficiency		65.5 % (60.5 – 70.5 %)

Table 14 shows that CD 100 had a specificity of 60.0%, sensitivity of 71.2% with a positive predictive value of 32.1%

TABLE 16: CD4 $\leq$ 200 as a prognostic test

CD4	DEAD	ALIVE
≤ 200	160	114
> 200	10	56
Prevalence	21.0 %	
Sensitivity	94.1 % (90.6 – 97.7 %)	
Specificity	32.9 % (25.9 – 40.0 %)	
Positive Predictive Value	27.2 %	
Negative Predictive Value	95.5 %	
Test Efficiency	63.5 % (58.4 – 68.6 %)	

The sensitivity for CD200 was 94.1%, specificity 32.9% and positive predictive value of 27.2%

TABLE 17: Combined Hb $\leq$ 9 and CD4 $\leq$ 100 as predictors of mortality

Hb$\leq$9 CD4$\leq$ 100	DEAD	ALIVE
YES	88	21
NO	82	149
Prevalence		21.0 %
Sensitivity		51.8 % (44.3 – 59.3 %)
Specificity		87.6 % (82.7 – 92.6 %)
Positive Predictive Value		52.7 %
Negative Predictive Value		87.2 %
Test Efficiency		69.7 % (64.8 – 74.6 %)

Hemoglobin of 9 and CD4 100 combined had a sensitivity of 51.8%, specificity of 87.6% and a positive predictive value of 52.7%.

TABLE 18: Combined Hb $\leq$ 9 and CD4 $\leq$ 200 as predictors of mortality

Hb $\leq$ 9 CD4 $\leq$ 200	DEAD	ALIVE
YES	112	36
NO	58	134
Prevalence	21.0%	
Sensitivity	65.9 % (58.8 – 73.0 %)	
Specificity	78.8 % (72.7 – 85.0 %)	
Positive Predictive Value	45.3 %	
Negative Predictive Value	89.7 %	
Test Efficiency	72.4 % (67.6 – 77.1 %)	

The combined parameters of hemoglobin 9 and CD4 200 had sensitivity of 65.9%, specificity of 78.8% and the positive predictive value of 45.3%

TABLE 19: Combined Hb ≤ 9 and WHO stage 3 as predictors of mortality

Hb ≤ 9 WHO stage 3	DEAD	ALIVE
YES	26	22
NO	144	148
Prevalence	21.0 %	
Sensitivity	15.3 % (9.9 – 20.7 %)	
Specificity	87.1 % (82.0 – 92.1 %)	
Positive Predictive Value	23.9 %	
Negative Predictive Value	79.5 %	
Test Efficiency	51.2 % (45.9 – 56.5 %)	

The sensitivity for combined hemoglobin 9 and WHO stage 3 was 15.3%, specificity was 87.1% and the positive predictive value of 23.9%. The negative predictive value was 79.5%.

TABLE 20: Combined Hb ≤ 9 and WHO stage 4 as predictors of mortality

Hb ≤ 9 WHO Stage 4	DEAD	ALIVE
YES	89	20
NO	81	150
Prevalence	21.0 %	
Sensitivity	52.4 % (44.8 – 59.9 %)	
Specificity	88.2 % (83.4 – 93.1 %)	
Positive Predictive Value	54.2 %	
Negative Predictive Value	87.4 %	
Test Efficiency	70.3 % (65.4 – 75.2 %)	

Combined hemoglobin 9 and WHO stage 4 had a sensitivity of 52.4%, specificity of 88.2% and a positive predictive value of 52.4%

TABLE 21: Combined Hb $\leq$ 9, WHO Stage 3 and CD4 $\leq$ 100 as predictors of mortality

Hb$\leq$ 9 WHO Stage 3 CD4$\leq$ 100	DEAD	ALIVE
YES	17	7
NO	153	163
Prevalence	21.0 %	
Sensitivity	10.0 % (5.5 – 14.5 %)	
Specificity	95.9 % (92.9 – 98.9 %)	
Positive Predictive Value	39.2 %	
Negative Predictive Value	80.0 %	
Test Efficiency	52.9 % (47.6 – 58.2 %)	

The combined parameters of hemoglobin 9, WHO stage 3 and CD4 200 had a low sensitivity of 10.0%, high specificity of 95.9% with a positive predictive value of 39.2%.

Table 22: Testing the agreement in predicting mortality between Hb, WHO and CD4 count

	CD4/WHO mortality	CD4/WHO alive	Total
Hb mortality	89	36	125
Hb alive	20	134	154
Total	109	170	279

Observed agreement = 0.79

Chance expected agreement = 0.511

Kappa = 0.589

P value = < 0.001

The percentage agreement was 0.79 and kappa was 0.589

DISCUSSION

Infection with HIV ultimately leads to profound immunosuppression in which patients may present with various AIDS defining clinical conditions that may impact negatively on the quality of life of the patients and may ultimately lead to death. However, the rates of disease progression among the patients vary widely.

The identification of the clinical and biological markers of disease progression to AIDS and death is important for the proper optimisation of the management of patients with HIV. The WHO staging system was published in 1990 and is based on clinical and biological parameters; it includes 32 clinical conditions divided in four stages and a laboratory axis with three CD4 cell count groups.

Several studies to evaluate and validate the WHO clinical staging system and the CD4 cell count levels have been done and correlation between the two and survival has been established. However, these studies need to be repeated since the progression to AIDS and death in HIV disease is dependent on many factors such as HIV variants, route of transmission, host immune system, nutritional status, anaemia and opportunistic infections, among others. Therefore in this study we are looking at the prognostic values of anemia, initial WHO clinical staging system and CD4 cell count in predicting mortality in a cohort of Zambian HIV patients enrolling in the ARVs programme.

A total of 340 HIV positive patients were included in this study and the laboratory markers of FBC and CD4 cell were done on all the patients, the WHO clinical staging was also clinically assessed for each patient and these were used to test the predictive values in predicting mortality in this cohort of patients.

The majority of patients were between the ages of 21 years and 50 years with the highest percentage being in the age group of 31 to 40 years (42.9%). This is the most productive and economically active age group. There was not much of a difference in the sex distribution of the study group though there were more females

(56.8%) than men. The majority of the patients were married (52.4%) and few were divorced. This raises the question of whether marriage is a risk factor in acquiring HIV infection in Zambia, if so what are the factors that influence this pattern? A total of 292 (85.9%) patients had received a minimum of primary education and 60.3% of the patients were in formal employment.

The level of anaemia in this study group was significantly high, that is, 282 patients (82.9%) had haemoglobin levels below 12g/dl. Anaemia is recognised to be a significant clinical problem in HIV disease (Jens DL and Amanda M, 2003). Despite the ability of anaemia to occur at any clinical stage of HIV, its frequency and severity are positively correlated to disease progression and death (Jeffrey SA and Isaac L et al, 2006). Various risk factors for HIV related anaemia have been identified such as clinical AIDS; CD4 cell counts < 200 cells per microlitre, female sex, African American ethnicity and high plasma viral load. In keeping with the above risk factors for anaemia, this study group had more females. All were Africans and the majority of patients in the study had CD4 levels below 200 cells (n =274, 80.6%), and 201 (59.1%) were in WHO clinical stage IV which is the AIDS stage. However, plasma viral loads were not done on the patients included in the study. This is so due to the prohibitive cost of the test in Zambia. Though it is done in some patients at their own expense whilst on the ARVs programme, it is not routinely done and therefore its effect on the levels of anaemia cannot be evaluated in this study.

The critical level of haemoglobin 9g/dl for calculating the predictive value of anaemia in predicting mortality in this study group was picked because it was the level at which both the sensitivity and specificity were nearest to each other statistically (Sensitivity 68.2% and Specificity 71.8%). The sensitivity was 68.2% and positive predictive value of 39.1% at 95% confidence interval. A total number of 116 (68.2%) patients died with haemoglobin equal to or less than 9g/dl whilst only 54 (31.8%) died with greater than 9g/dl from among the deceased group of the study. Among the patients who were alive 48 (28.2%) had haemoglobin below

9g/dl and the rest of the patients had hemoglobin levels higher than 9g/dl. This finding correlates well with other studies done that show that anaemia is associated with reduced survival. A study done by Stringer et al in Lusaka urban district clinics showed that most of the patients with haemoglobin equal to or less than 8g/dl were associated with increased likelihood of mortality (Stringer et al 2006). Another study by Kiros et al showed that anaemia is associated with increased mortality (Kiros B et al., 2004). The EuroSIDA study also found that anaemia was highly associated with a much faster rate of disease progression and mortality. In the EuroSIDA study anaemia was found to be an independent predictive marker for clinical prognosis in HIV infected patients. In the same study, 40.8% patients with haemoglobin of less than 9g/dl died as opposed to 3.1% of patients without anaemia. In this study, 119 patients (34.1%) with hemoglobin less than, or equal to 9g/dl died, as compared to 54 patients (15.9%) with haemoglobin above 9g/dl who also died. Anaemia highly contributes to mortality in our setting among patients with HIV despite the relatively not so high specificity (68.2%) in predicting mortality among our cohort of HIV patients. Among this group of patients that are alive, only 48 (14.1%) had haemoglobin levels below 9g/dl.

Most of the patients in our study group were in WHO clinical stages 3 and 4 (n = 315, 92.6%), with few presenting in WHO clinical stages 1 and 2 (n = 25, 7.4%). The majority of the patients in the study therefore were in the late stages of the disease. This could be so because the site of the study is a referral hospital and as such delays in referring patients from the clinics could lead to their being presented to the hospital at a late stage. The other contributing factors could be differences in participant's memory of previous ailments and lack of laboratory facilities needed in the diagnosis of certain ailments such as CMV infections. Despite the above constraints, sufficient care was taken in getting the medical history of the patients which included collecting information from the next of kin to the patient or the person who has been caring for the patient during the period of the illness. Physical examination, the availability of CD4 measurements and other laboratory facilities were used to accurately evaluate the condition of the patient.

In predicting mortality, the WHO clinical stage 4 has a sensitivity of 77.7%, specificity of 59.4% and PPV of 33.7% at 95% confidence interval (CI). The WHO clinical stage 3 has sensitivity of 21.8% and specificity of 54.7% and PPV of 11.3% at 95% CI. Combined WHO clinical stages 3 and 4 have a sensitivity of 99.4%, specificity of 14.1% and PPV of 23.5% at 95% CI. A total of 132 patients in WHO clinical stage 4 died, 37 patients in WHO clinical stage 3 died as compared to only 1 patient in WHO clinical stage 2 who died and no patient in WHO clinical stage 1 died. Therefore WHO clinical stage 4 had the highest number of mortalities followed by WHO stage 3. As such these stages were associated with the highest numbers of mortalities and the initial WHO clinical stage is an independent risk factor for mortality.

It is therefore important to evaluate our patients fully and to determine the WHO clinical staging even though we may have no much laboratory backup in diagnosing of some of the illnesses in WHO clinical stage 3 and 4 in HIV patients as this stage has an important prognostic value.

In the Zambian study by Stringer et al it was found that WHO clinical stages 3 and 4 were associated with the likelihood of death in their cohort of patients with the initial WHO clinical stage at enrolment for starting HAART being an independent risk factor for mortality (Jeffrey SA and Isaac Z et al, 2006). Elias Kassa and colleagues in Ethiopia also found that the initial WHO clinical staging of HIV disease was a good prognostic marker among a cohort of HIV patients. In their study, WHO clinical stages 3 and 4 were associated with the highest mortalities, even though the study design was different from our design. Similar results were obtained in regard to the likelihood of mortality in these stages of the disease (Elias K and Tobias FR et al, 1999, David V and Neil G et al, 1998). Samuel SM et al in a study in rural Uganda among a cohort of HIV patients also found that even without laboratory markers, the clinical category of the WHO clinical staging was a useful predictor of survival in individuals with HIV disease. Patients with WHO clinical

stages 3 and 4 had the shortest survival period (Samuel SM and Dilys M et al, 1999).

In this study 110 (32.4%) patients had CD4 count less than or equal to 50 cells per microlitre. Of these 72 patients (21.2%) were among the dead and 38 (11.2%) patients among the living cohort. At CD4 100 cells per microlitre there were 189 (55.6%) patients. Of these 121 patients (35.6%) had died and 68 patients (20%) were among the living cohort. A total of 274 patients (80.6%) had CD4 less than or equal to 200 cells per microlitre, 160 patients (47.1%) were among the dead and 114 (33.5%) were among the living group. This, therefore, shows that most of the patients in the study had CD4 that are less than or equal to 200 cells per microlitre with relatively few patients with CD4 counts that are equal to or less than 50 cells per microlitre. More patients (47.1%) with below CD4 200 cells per microlitre died as compared to other CD4 levels.

The prognostic values of CD4 count levels in predicting mortalities were as follows CD4 50 has a sensitivity of 42.4%, specificity of 77.6% and PPV of 33.5%; CD4 100 has a sensitivity of 71.2%, specificity of 60.0% and PPV of 32.1%; CD4 200 has a sensitivity of 94.1%, specificity of 32.9% and PPV of 27.2%.

The CD4 count had the highest sensitivity of 94.1% in predicting mortality at CD4 200 despite the other CD4 levels of 100 and 50 having relatively low sensitivities of 71.2% and 42.4%, respectively. This therefore shows that CD4 count is a good predictor of mortality among HIV infected patients.

According to the Zambian guidelines for administering ART, antiretroviral drugs (ARVs) are initiated in individuals with either a CD4 cell count less than 200 cells per microlitre or WHO stages 3 or 4, or patients in WHO stages 1 or 2 but with CD4 cell count equal to or lower than 200. (WHO/UNAIDS, 1998).

In this study mortality was highest at these parameters. The study by Stringer et al in Lusaka found that CD4 ranges of 50 – 199 and WHO clinical stages 3 and 4 were strongly associated with mortality. In another study by Anastos K et al to determine the prognostic values of CD4 cell counts, it was also found that reduced CD4 cell counts were associated with increased mortality (Anastos K et al, 2004, Jeffrey SA and Isaac Z et al, 2006). In the Women's Interagency HIV Study Kiros et al found that CD4 count of less than 200 cells was associated with decreased survival in their cohort of patients. Another of their findings was that patients with CD4 less than 200 were more likely to be anemic (Kiros B et al., 2004). This was also reflected in our study. David et al in the study of prognostic indicators for AIDS and infectious disease death in HIV infected drug users it was found that CD4 cell count of below 200 and HIV viral load were powerful prognostic indicator for disease progression and death independently (David V and Neil G et al, 1998). However in this study, the viral load was not measured due to the cost of the laboratory test

When the parameters of haemoglobin, WHO clinical staging and CD4 count were combined, the highest sensitivity (65.9%) was found to be that of haemoglobin less than 9g/dl and CD4 less than 200 cells per microlitre. This is in comparison to the other parameters that were measured. This was also associated with the highest mortalities (32.9%). The WHO clinical stage 4 and haemoglobin less than 9g/dl were also associated with significant mortality. This has a sensitivity of 52.4% and PPV of 54.2%. These findings therefore mean that in the patients that are assessed for ART treatment, particular care and close monitoring is needed as these patients are at risk of increased chances of mortality. Jensen et al, in comparing low mortality among HIV infected individuals with that of the general population, found that low CD4 of less than 200 was associated with high mortality rates even when such patients were started on HAART (Jens DL and Amanda M, 2003). Stringer et al also found that low CD4 counts, anaemia and WHO clinical stages 3 and 4 are associated with increased chances of mortality among HIV patients in Lusaka (Stringer et al 2006). Kiros also found that anaemia and CD4 less than 200 are

associated with increased mortality (Salot Y et al., 1997, Soren JF and Lars P et al, 2004, Kiros B et al., 2004)

The observed agreement of haemoglobin, WHO clinical staging and CD4 cell count, was 0.79 and kappa was 0.589. Therefore, the agreement between Hb, WHO clinical staging and CD4 cell count in predicting mortality was good.

These findings show that the parameters of haemoglobin level, WHO clinical staging and CD4 count, can be used to identify patients with the highest risk of mortality in the care of HIV patients. The WHO clinical staging is also a good predictor of mortality even in resource limited areas despite the lack of sophisticated equipment used in the diagnosis of certain illnesses in advanced HIV disease

LIMITATIONS OF THE STUDY

This study has some limitations. Firstly, viral loads were not done on all the patients. Viral load is considered as a more reliable marker of disease progression and doing the test would have offered more information on our patients.

Secondly, only a FBC was done and in some instances the indices of a full blood count were missing especially of the deceased group of patients thereby making it difficult to compare such parameters. Bone marrow biopsy and peripheral smears were not done on any of the study group patients.

Thirdly, the parameters that were used were the initial ones only. A follow up with serial FBC, CD4 and WHO done at selected intervals would have given a more comprehensive picture.

CONCLUSION

The levels of anaemia among patients with HIV enrolling on the ART programme at UTH are significantly high at 82.9%. Anaemia in HIV disease is associated with the highest likelihood of mortality irrespective of the cause.

The level of haemoglobin in HIV disease can be used to identify patients with the highest risk of mortality. In this study, haemoglobin equal to or less than 9g/dl had a sensitivity of 68.2% with a positive predictive value of 39.1% in predicting mortality among HIV patients.

CD4 cell count below 200 cells per microlitre had the highest sensitivity of 94.1% in predicting mortality but had a low positive predictive value of 27.2%. This therefore, means that though CD4 count is a good predictor of mortality, there could be a number of false positives. Lower CD4 especially counts those below 200 cells per microlitre were associated with high mortalities

WHO clinical staging was found to be a good predictor of mortality in our study, with sensitivities as high as 77.6% at Stage 4. Most of our patients were in WHO clinical stages 3 and 4 with very few patients in stages 1 and 2. WHO clinical stages 3 and 4 were associated with high mortalities in this study.

Haemoglobin level combined with CD4 levels had low sensitivities in predicting mortality of between 51.8% and 65.9% at haemoglobin 9g/dl and CD4 100 and 200 respectively. Similarly, a combination of haemoglobin level and the WHO clinical staging; haemoglobin level, WHO clinical staging and CD4 staging had relatively low sensitivities

RECOMMENDATIONS

1. Screening of patients for anaemia should be strengthened in all centers that are offering ART services.
2. The patients with haemoglobin levels equal to or less than 9g/dl should be closely monitored, cause of anemia identified and quickly treated as these patients are more likely to demise irrespective of the cause of anaemia.
3. Patients with CD4 counts lower than 200 have a high likelihood of mortality. The CD4 count is a good predictor of mortality in HIV patients, therefore patients with such levels of CD4 need close monitoring even when they are commenced on HAART.
4. WHO staging system should be assessed in all patients before commencing them on HAART as it is a good predictor of mortality. Those in stages 3 and 4 should be closely monitored, opportunistic infections identified and treated so as to try and reduce the mortality levels at those stages of HIV disease.
5. Patients with CD4 below 200, low haemoglobin below 9g/dl and WHO clinical stages 3 and 4 need very close monitoring when initiating them on ARVs as such patients have a high risk of mortality.
6. Haemoglobin level and WHO clinical staging system can be used to identify patients at high risk of mortality in resource limited areas where there are no facilities for CD4 counts and viral loads. These have been found to be good predictors of mortality in HIV patients in our study.

FUTURE RESEARCH

Future research should focus on

1. Furthering the understanding of the causes of anaemia and its long term impact in HIV infection.
2. The impact of various HAART regimens on the prevalence of anaemia in HIV.
3. The use of epoetin alfa and the optimal dosing strategies in the treatment of anaemia in HIV.

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APPENDIX I

THE PREDICTIE VALUE OF ANAEMIA IN DETERMINING MORTALITY IN HIV DISEASE

STUDY #: _____ DATE: ____/____/____

ALIVE/ DEAD: _____ AGE: ____ DOB: ____/____/____

SEX: M/F UTH FILE No. _____ DMD No. _____

MARITAL STATUS: SINGLE/MARRIED/DIVORCED/WIDOWED

EDUCATIONAL LEVEL: None/Primary/Secondary/Tertiary

OCCUPATION: Unemployed/Government/Private/Self
Specify: _____

DATE TESTED POSITIVE ____/____/____ Place: _____

SYMPTOMS: _____

PHYSICAL
EXAMINATION: Temp: ____ Weight: ____ BP: ____ Pulse: ____

General Appearance: Wasted/Not wasted

- Pallor : Yes/No
- Jaundice : Yes/No
- Oral Cavity : Candida/Kaposis Sarcoma/Others _____
- Lymph nodes : _____
- Heart : _____
- Lungs : _____
- Abdomen : _____

Skin : _____

Urogenital : _____

Musculoskeletal: _____

Neurological : _____

Other (Specify): _____

DIAGNOSIS : 1. _____

2. _____

3. _____

4. _____

5. _____

WHO HIV STAGE: 1. 2. 3. 4.

Stage 1

- ☐ Asymptomatic HIV infection
- ☐ Persistent gen.lymphadenopathy

Stage 2

- ☐ Herpes Zoster (last 5 years)
- ☐ Sores/cracks around lips
- ☐ Recurrent mouth ulcers
- ☐ Itching rash
- ☐ Recurrent URIs
- ☐ Esophageal thrush

Stage 3

- ☐ Severe bacterial inf (muscle, pneu.)
- ☐ Oral thrush/hairy leukoplakia
- ☐ > 1 mo.diarrhea, vag. Candida, fever
- ☐ Tuberculosis, pulm.(in last year)
- ☐ Wt loss>10% body wt. no diarrhea, fever

Stage 4

- ☐ HIV Wasting Syndrome (>10% wt loss and >1 mo diarrhea and >1 mo fever).
- ☐ Herpes, oral/vag > 1 mo
- ☐ Lymphoma
- ☐ Kaposi's Sarcoma
- ☐ Invasive Cervical CA
- ☐ PCP
- ☐ Tuberculosis, extrapulmonary
- ☐ Cryptococcal meningitis
- ☐ HIV encephalopathy

MEDICAL HISTORY

<u>DIAGNOSIS</u>	<u>YEAR/DATE DX</u>	<u>TREATED YES/NO</u>
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

DRUG HISTORY:

<u>NAME OF DRUG</u>	<u>DATE PRESCRIBED</u>	<u>DURATION</u>
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

PLAN

INVESTIGATIONS DONE

NONE _____
HAEMOGLOBIN _____
FULL BLOOD COUNT _____
CD4 Count/Viral Load _____

TREATMENT GIVEN

- i) Antibiotics (specify): _____
- ii) Antihelmitiths: _____
- iii) Haematemics: FeSO₄/Folic acid/others _____
- iv) Blood transfusion: Yes/No if yes No. of pints _____
- v) Antituberculous treatment: _____

- VI) ARVs (Specify): _____

Was any drug changed due to worsening anaemia? Yes/No



If yes, Specify: _____

New drug substituted: _____

Has patient's anaemia improved after change of drug? Yes/No

If No. what was done _____

FINAL OUTCOME

- i) Dead: _____
Cause of death _____
Treatment before death _____
- ii) Alive: _____
Current treatment _____
- iii) Hospitalised: _____ Diagnosis _____

Last haemoglobin and CD4 Count before final outcome:

Haemoglobin: _____
Others done: _____

CD4 Count: _____
Others done: _____

Weight before outcome: _____

WHO Stage before outcome: _____

Viral Load: _____

APPENDIX II

INFORMATION SHEET

- 1 This is a research study aiming at finding the role anemia plays in HIV disease during the course of the disease. Anemia is a condition in which an individual has low blood (low Hb) and is a common feature associated with HIV disease. Investigations done have shown that anemia affects the quality of life of HIV patients, but the predictive values of anemia in identifying patients with the highest risk of mortality have not yet been evaluated.
2. The study is therefore being done to establish the predictive value of the level of hemoglobin (Hb) in predicting the outcome i.e. whether a patient is likely to die or live during the course of the disease. This will be of value in that those found to be at risk of death could be treated promptly and adequately so as to improve the chances of survival of such patients. This will be possible if a relationship is established between anemia and death.
3. Enrolment in this study will mean that the investigator will have access to your medical records, extract all the necessary information needed and entered onto a questionnaire.
4. Participation in this study is voluntary and one may choose to withdraw at any time without suffering any penalty or losing any of the patient's rights in receiving medical care.
5. The investigator might decide to terminate a person's participation into the study when circumstances dictate it, for the best result of the study.
6. Agreement to take part in this study does not place any obligation to the investigator or the hospital authorities other than that due to any other patient at the hospital.
7. Records will be identified by a study number not by the participants name, the two will be unlinked in order to safeguard confidentiality. The information extracted from the

participants medical records will not be used for their detriment. Their names will not be used in any report.

8. The study final report will be accessible in the event one might be interested to know the study results.

APPENDIX III
THE PREDICTIVE VALUE OF ANAEMIA IN DETERMINING MORTALITY IN HIV DISEASE.

CONSENT FORM

I, have received and understood clearly the explanations and purposes of this study of the role anaemia plays in predicting the clinical outcome of HIV disease.

The study is taking place at Phase V Medical admission ward, medical E wards and medical clinic 5.

Enrolling in this study will include having access to my medical records and investigations results that I have under taken including the HIV test. All the information will remain confidential and will never be made available for any other purpose other than the study.

I am free to participate or refuse to participate in the study and this will not interfere with the care I will receive at the hospital and can withdraw from the study at any point. The agreement to take part in this study does not place any obligation to the investigator or the hospital authorities other than that due to any other patient at the hospital. In the event that I am interested to know the study results, the study final report will be made accessible to me.

I understand that the study does not violate my personal rights and conscious in any way. In signing this document I agree that I do so voluntarily and I am under no coercion from anyone.

Patient's Signature/thumb print:..... Date:.....

Witness name:.....Signature:.....Date.....

8. Contact persons are:

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