UNIVERSITY OF MALAWI

College of Medicine

Relationship Between WHO Staging and CD4 Cell Count in Patients Receiving Antiretroviral Therapy at Mzuzu Central Hospital

By

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CERTIFICATE OF APPROVAL

The Thesis of Tulipoka Nellie Soko is approved by the Thesis Examining Committee

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DECLARATION

I Tulipoka Nellie Soko hereby declare that this thesis is a result of my original work and has not been presented for any other awards at the University of Malawi or any other University.

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ABSTRACT

BACKGROUND: There are different recommendations on how to initiate Anti retroviral therapy (ART). Most of these recommendations require evidence of immunological deterioration for one to start ART. In Malawi, initiating ART is usually based on a positive HIV test and clinical staging using a W.H.O staging system.

RATIONALE: There is limited data locally or internationally that has looked at the validity of using WHO staging as the sole entry point to an ART program and also limited data in using only clinical parameters to determine good response of its ART recipients.

METHODS: A retrospective descriptive audit of 230 HIV positive patients' records that had completed one year of ART at the Rainbow clinic in Mzuzu Central Hospital.

RESULTS: At the start of ART, 29 patients were in WHO stages 1 and 2, 154 were in stage 3 and 47 in stage 4. CD4 count range for all stages was 1- 1062 cells/mm^3. Initial mean CD4 counts were 152, 188, and 140 for WHO stages 1 &2, 3 and 4 respectively and initial mean BMI values were 21, 19 and 20 for WHO stages 1&2, 3 and 4 respectively. Patients in all WHO stages showed some significant increase in both CD4 cell counts and BMI over the 4 monthly follow up to 12 months p value less than 0.05.

CONCLUSION: A patient's WHO stage at the start of ART does not seem to reflect the severity of immune-depression

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ACRONYMS

AIDS	Acquired immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
ARV	Anti Retroviral (drug)
BMI	Body Mass Index
CD4 cells	subgroup of T-lymphocytes carrying CD4 antigens
CHAM	Christian Hospitals Association of Malawi
COMREC	College of Medicine Research Committee
DALYs	Disability Adjusted Life Years
HIV	Human Immunodeficiency Virus
KCH	Kamuzu Central Hospital
MoH	Ministry of Health
NAC	National AIDS Commission
NSO	National Statistics Office
PMTCT	Prevention of Mother to Child Transmission (of HIV)
QECH	Queen Elizabeth Central Hospital
UNAIDS	Joint United Nations Programme on HIV/AIDS
W.H.O	World Health Organization

CHAPTER 1

INTRODUCTION

Human Immunodeficiency Virus type 1 (HIV-1) is the virus responsible for the global HIV pandemic. HIV primarily infects and destroys cells in the immune system particularly CD4+ T-lymphocytes. The degeneration of the immune system over the years, results in increased risk of opportunistic infections and malignancies and this is the hallmark of Acquired Immune Deficiency Syndrome (AIDS). The rate at which the immune system is destroyed is directly related to the rate of viral replication.

In developed countries, the initiation of Anti-Retroviral Therapy (ART) is usually based on laboratory measurements of CD4 T-cell lymphocyte count a test that acts as a proxy for immune status. Levels of 200-500 cells/ mm^3 constitute moderate immune suppression, less than 200 cells/ mm^3 is advanced while as less than 50 cells/ mm^3 constitute severe immune suppression respectively. Knowledge of CD4 cell counts therefore indicates the stage of disease the patient has reached, allows for providers implementation of early initiation of ART including primary prophylaxis against opportunistic pathogens, common bacterial infections and enteritis.

The World Health Organization (WHO) (2002) recommends that all patients with a CD4 count less than 250 cells/mm^3 should be considered eligible for ART. However, in most developing countries where resources are limited, the

decision to start ART is usually based on clinical symptoms and WHO staging alone. A number of studies support the WHO clinical staging system, including studies in resource constrained countries. Farmer et al (2001) has reported an innovative strategy that relies on syndromic recognition of symptomatic HIV disease as an indicator for starting ART.

A cross-sectional study of 86 Ethiopians with an HIV infection reported a good correlation between WHO stages and CD4 T lymphocyte counts (Crowe, 2003).

In Malawi, there is limited data on the relationship between the clinical symptoms and CD4count levels. Mzuzu Central Hospitals' Rainbow Clinic has been able to carry out CD4 count testing on patients starting and continuing on ART. A retrospective audit of the ART program at the Rainbow clinic was therefore conducted to assess the relationship between WHO clinical staging and CD4 count. The study specifically involved reviewing patients' case notes of those who attended the clinic between the months of January to June 2005, then continued for a total period of 12 months.

1.2. Background literature review

1.2.1. The HIV epidemic in Southern Africa

The HIV/AIDS epidemic has become a major problem worldwide with an estimated 40 million people living with the virus by the end of 2004 (UNAIDS 2004). The Southern African Region is at the epicenter of the HIV/AIDS epidemic. It is estimated that by the end of 2005, 26 million people were living with HIV in the region, 3.2 million were newly infected, 85% of all adult deaths were attributable to HIV (UNAIDS 2005). Jaffer (2005), also states that the majority of hospital admissions in many countries are attributed to AIDS. UNAIDS report (2005), reveals that HIV has been responsible for the reduction in the life expectancy in this region from 47 years in 1987 to 40 years in 2001, In addition, it is estimated that about 11 million children are orphaned by AIDS.

HIV infection causes a progressive decline in cell-mediated immunity as evidenced by a decrease in the number of T-cell lymphocytes that bear the CD4 receptors in most HIV infected individuals. The use of ART improves the survival of patients living with HIV. As a result of this, HIV infected individuals live longer and lead a more productive life. The use of ART is therefore considered central to AIDS- treatment and prevention (OPC/NAC 2003).

In affluent countries like Europe, North America, and even Brazil, the decision to start ART is based on information on CD4 cell count, viral load as well as resistance testing to determine eligibility and the best regimen for the HIV positive patients. These developed countries use a specialized approach of frequent laboratory testing to monitor the HIV positive patients' immune status, drug side effects and the development of drug resistance (Hargreaves 2002). This is because the effectiveness of ART is most commonly measured by the degree of control of HIV replication as indicated by the viral load. Goidestein, (1997) states that the success of antiretroviral therapy depends on early diagnosis, appropriate care and support from significant others. Kent (2003), recommend that monitoring of HIV infection must include routine clinical assessment and measurement of CD4 count and plasma HIV load.

Use of ART has been shown to drop viral load to undetectable levels, provide effective inhibition of HIV-1 replication, decrease number of opportunistic infections, including consequent number of admissions to hospitals, as well as AIDS related deaths (Hammer, 1997). Lamptey (2006), also states that mortality due to AIDS has dropped precipitously partly because of access to the cost-effective ART such that, AIDS has become for many individuals a chronic illness. Some of these findings have now been replicated in developing or middle income countries. A study conducted in Thailand

showed that patients treated with ART responded as well as those from developed countries (Ungsedhapand, 2001).

In 2002, W.H.O. estimated that 6 million people were in need of life sustaining ART in the developing world. In most of these developing countries, resources are limited and laboratory tests are inaccessible to majority of people as a result, the decision to start ART usually relies on syndromic recognition of symptomatic HIV disease and clinical indicators like severe weight loss in absence of Tuberculosis (TB), repeated opportunistic infections unresponsive to antibacterial and antifungal treatment, or typical neurological complications of HIV such as encephalopathy, distal sensory or other neuropathies (Kent, 2003).

In a study conducted jointly by the Salvation army and college of medicine in Bangwe on Home based care, findings reveal that the most commonly reported symptoms by AIDS patients at first assessment include the following; headache, fever, severe weight loss and respiratory problems (Geubbles,2006). These assessments are mostly done by medical interview and examination as a result the process prioritizes patients with symptomatic HIV disease. Secondly, where medical resources are limited, the use of WHO clinical stage over CD4 count for identifying those patients who will benefit most from ART allows therapy to be targeted to symptomatic individuals who are already likely to be seeking care within the health system (Kent, 2003).

1.2.2. Malawi's response to the HIV/AIDS epidemic

In Malawi, the response to the HIV epidemic began as early as 1986. Initial efforts were concentrated on preventing transmission of HIV using the Abstinence, Be faithful, use a Condom (ABC) approach. Since then, HIV has been termed as the dominant cause of disease burden in Malawi for it accounts for 31% of the total burden as measured in Disability Adjusted Life Years (DALYs) (Geubbels, 2006). The HIV epidemic has also resulted in increased morbidity and mortality rate as well as reduced economic productivity among its citizens.

Currently, it is estimated that HIV prevalence rate in adults aged 15 to 49 years is at 15% (95% CI: 12%-17%) (NAC, 2003) the HIV prevalence rate is higher among women (13%) than among men (10%) (NSO, 2005). One of the reasons could be due to the very nature of the biological differences between men and women considering that the heterosexual route remains the major mode of HIV transmission of which it accounts for 90 percent of HIV cases in the country. The risk of transmission from one infected person to another per coital act is currently estimated at 0.0011 (95% CI 0.0008-0.0015) (Geubbles, 2006) as such, during unprotected sexual intercourse, women are more exposed to the virus due to large surface area that comes in contact with semen (MANET, 2003).

Muula (2003), reports that there are an estimated 400,000 AIDS related orphans 70,000 of whom are infected themselves. NAC (2005), states that of the 1 million people living with HIV/AIDS, 185,000 people require antiretroviral therapy. Malawi started offering ARVs at a fee in the year 2000. These ARV's were being offered to eligible patients at designated hospitals which had attained the required set standards for offering ART (MOH 2003). By the year 2002, ARVs were initially provided in the 3 institutions which were two central and one district hospitals namely Queen Elizabeth Central Hospital (QECH) in Blantyre, Kamuzu Central Hospital (KCH) in Lilongwe and Chiradzulu District hospital (Van Oosterhout, 2005).

The country has since then scaled up the provision of ART in response to the WHO 3 by 5 campaigns such that from this drastic scale up, ARV's have become free of charge such that by the end of 2005, there were a total of 139 facilities in public, Christian Health Association of Malawi (CHAM) and private sectors delivering ART using the national system. By June 2006, there were 57,366 patients who were receiving ART in Malawi (MOH 2006).Findings from an ongoing audit conducted at QECH in Blantyre, revealed that patients who took their treatment faithfully responded well to treatment (Van Oosterhout, 2005). While some previous studies have established the importance of using CD4 count as entry criteria for starting ART, one is aware of the high numbers of patients requiring ART in the

country, the scarcity of health facilities offering CD4 count services and the cost to the whole system.

In Malawi, records reveal that by June 2006, out of 139 facilities providing ART, only14 (10%) had the capacity to perform CD4 counts specifically restricting mostly to HIV infected children and HIV positive pregnant women identified through prevention of mother to child transmission of HIV (PMTCT) programme and of whom on clinical staging, are not eligible for ART (MOH, 2006). As a result of this shortage, most health facilities rely on using WHO clinical staging alone to initiate patients on ART and clinical findings to monitor patients' response to ART. What we do not know is the outcome to those that wait for a long time to reach WHO stage 3 and 4 before they start treatment.

1.2.3. Indicators for initiating ART

HIV infection is almost always fatal without treatment although a few individuals have survived with HIV infection untreated for up to 20 years. Since the introduction of ART in 1996, the drug therapy has transformed HIV from a progressive terminal illness to a manageable chronic disease (Lamptey, 2006).

The goals of ART include the following:

1) prolongation of life and improvement in the quality of life

2) greatest possible reduction of viral load preferably to undetectable levels to halt disease progression

3) Possible reconstitution of the patients immune system both quantitatively and qualitatively

4) rational drug use so as to achieve immunological, clinical and virological goals

5) reduction in HIV transmission (Gallants, 2003).

Patients are asked to start ART to achieve the five goals listed above but the overriding one is improving the life of the patient in order to remain productive members of their communities and also help reduce the number of orphans and vulnerable children.

Several groupings and organizations have produced guidelines on when to start ART. (www.aidsinfo.nih.gov). The Department of Health and Human Services (DHHS) in the United States guidelines recommend the use of CD4 count and viral load testing as the most important indicator to determine who starts ART. Furthermore, the DHHS guideline also mentions that anybody with symptoms caused by HIV (i.e. WHO stages 2, 3 and 4) should start ART. These recommendations are based also on patients' readiness and willingness to start therapy including an understanding of adherence (Gallant, 2003). The WHO guidelines on Scaling up antiretroviral therapy in resource limited settings (2002), recommend using CD4 count as the entry point for ART although use of other measures like clinical staging and or a

total lymphocyte count is also advocated where CD4 count testing is not available.

1.2.4. The Malawi ARV treatment guidelines

The Malawi government adopted a public health approach in coming up with recommendations for the scaling up ART. The country uses the ARV treatment guideline which is the main document that outlines ways on how to provide ART in the service delivery areas. The main reference material for its recommendations was the WHO guidelines (2002) which classifies patients into 4 clinical stages according to clinical manifestations and individuals performance.

The document stipulates that WHO Stage 1 is an asymptomatic person with normal activity or those with acute infection, while as WHO stage 2 to 4 include patients with increasing clinical symptoms and decreasing performance. According to the Malawi treatment guidelines for HIV/AIDS 2nd edition, The program uses WHO guidelines for recruiting patients who have been confirmed to have a positive HIV antibody test obtained by using two rapid tests such as enzyme-linked immuno absorbent assay (ELISA), Western Blot or rapid test devices, staging of the patient's status using WHO clinical staging criteria and also having one of the following conditions:

Known to be HIV seropositive, understand the implications of ART. Then they have to be assessed and be in WHO clinical stage 3 or 4 or be in WHO

clinical stage 1 or 2 with a CD4 count below 250 cells/ mm^3 (NAC/MOH, 2006).

Most providers use the same clinical guidelines and improvement of symptoms to monitor progress of treatment. In the health facilities, patients that have suffered from WHO stage 3 or 4 conditions and understand the implications of ART use are eligible to start ART. These patients are given a first line regime of a fixed dose of stavudine (DT4) + lamivudine (3TC) + nevirapine (NVP). For those patients who are still in stage 1 or 2 and in the absence of CD4 cell count results are not eligible to start ART.

What is not clear is whether this policy correctly identifies those in need of ART firstly considering that some patients with severe immuno depression may remain relatively well without showing any signs and symptoms. Secondly, most clinicians conduct WHO staging at the health facility level and yet many patients report to these health facilities late when they are already showing signs and symptoms of advanced stages of clinical disease due to immunosuppression. A study by Hatchett (2004) on health seeking behaviour for AIDS in Malawi also revealed that western medicine is sought as a last resort after traditional remedies have failed. As a result of these scenarios, management of these individuals in the late stage of disease progression becomes complicated and treatment outcome is less likely to be successful (Arendt, 2007).

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1.3. Rationale of the study

Malawi is faced with a challenge in providing ART to an ever increasing number of patients. Estimates vary but in 2005 there was a projection that more than 180,000 Malawians require ART. However, due to resource constraints such as lack of adequate laboratory facilities for providing CD4 counts, the national ART program took a pragmatic approach to use the WHO staging as the main entry criterion for those patients requiring ART and clinical findings like BMI is often used as part of routine assessment of monitoring response to therapy. What is not clear is whether this pragmatic approach correctly identifies those in need of ART. Furthermore, there are no local data to assess the immunological status of patients in stage 1 or 2 to make them defer ART.

The purpose of this study was to establish whether there is a relationship between W.H.O clinical staging and CD4 count in HIV positive patients receiving antiretroviral therapy at Mzuzu Central Hospital's Rainbow clinic. In addition, the study was to assess if changes in CD4 count after initiating ART were associated with changes in BMI. Furthermore, this study was also intended to test the hypothesis that individuals starting ART in WHO stages 3 and 4 will have lower mean CD4 cell counts at the same time suffer a higher mortality compared to individuals in WHO stages 1 and 2.

CHAPTER 2

STUDY OBJECTIVES

2.1 Broad objective

The main objective of the study was to determine the relationship between W.H.O clinical stages to CD4 cell count in patients receiving ART at Mzuzu Central Hospitals' Rainbow clinic.

2.2 Specific objectives

The specific objectives of the study were as follows:

- To describe the socio- demographic characteristics of patients starting ART at the Rainbow clinic in Mzuzu
- To assess the relationship between CD4 count and BMI by WHO stage over 12 months in patients receiving ART at Rainbow clinic
- To compare 12 months mortality rates between the various W.H.O stages.

CHAPTER 3

STUDY METHODOLOHY

3.1 Study design

This was a retrospective descriptive study of auditing HIV positive patient's case records kept at the Rainbow ART clinic at Mzuzu Central Hospital.

By June 2005 of the 776 HIV positive patients who had registered for ART at the Rainbow clinic, 230 patients had met the criteria of the study and they were selected. Data of interest was abstracted on to data collection tool (Appendix 2). This data of interest at initiation of ART included socio-demographic details like sex, age, occupation, examination results of weight, height, WHO clinical staging and laboratory results of CD4 cell count. On follow up care, data was collected on BMI and CD4 counts at 4, 8 and 12 months. Finally patient outcome was recorded during the 12 months period of ART use in order to check whether the patient was still alive or dead and whether had defaulted treatment or else had transferred out to other facilities.

3.2 Study place

The study was conducted at Mzuzu central hospital, a government referral and teaching hospital situated in the Northern region of Malawi. This hospital serves both rural and urban population and provides free primary, secondary and tertiary level inpatient and outpatient services. The hospital

has an intergrated voluntary counseling and HIV testing units offered to those clients who wish to know their status.

3.3. Study population

Two hundred and thirty case files of HIV infected patients that started ART at Mzuzu Central Hospital between January and June 2005 and had complete data on socio-demographic details, examinations of weight, height and laboratory findings of CD4 values on initial and follow up, were included in the study. At this Rainbow clinic, patients were initially followed up every month for first two months thereafter it was every two months using both clinical assessment and laboratory monitoring of CD4 count in order to assess response to treatment intervention.

CD4 count was done using a FACS-Count instrument (Becton Dickinson, Immunocytometry Systems, San Jose, CA, USA) a simpler, automated cytometer adapted for clinical laboratories that quantifies CD4 cell counts.

Inclusion criteria was for all patients presenting at Mzuzu Central hospital ARV clinic who had their height, weight, BMI and CD4 checked before starting ART. The study included those patients living, dead or dropped out from treatment. An exclusion criterion was for all patients who started ART prior to commencement of ART at Mzuzu Central hospitals including those patients who were transferred in from other health facilities.

3.4. Study period

The study was carried out between December 2005 and December 2006 this was for a total period of 12 months. Activities conducted during this study period included the following:

- Literature search and review was done using Medline and internet search of publications on HIV/AIDS,
- formulating research question
- Developing a research proposal for submission to COMREC,
- Development of a monitoring tool for data collection,
- Recruiting and training the research assistant on how to use the instrument,
- Pre-testing the data collection tool,
- Data collection of data,
- Analyzing the data and
- Writing report on the findings (Appendix 1).

3.5. Sample size

Out of a total of 460 eligible patients' case notes, a systematic sample of every alternate file was pulled aside for evaluation such that by the end of the exercise, a sample size of 230 was arrived at for the study.

3.6. Data collection

Data was collected using a specific checklist (Appendix 2). The checklists included the following variables: age, sex, occupation, initial weight and height, WHO staging, CD4count results and patient outcome. Patients were not identified by name. Data was collected using special code numbers which were already being used at this clinic.

Prior to data collection, the research assistant was oriented on the research project and data collection tools. The orientation was done for two days at the Mzuzu central hospital. Two people namely the Principal investigator and the research assistant collected data from patients' files. During data collection, in order to enhance security and confidentiality, files were being kept securely in a locked filling cabinet. Data was coded in the computer using Microsoft Excel package and checked continuously for consistency. Electronic data was protected using a secret password. Data collection lasted for one month.

3.7. Data entry

Data entry was done using Epi info soft ware version 3.3.2 of 2005. (Centre for disease control and prevention, Atlanta CA, USA).

3.8. Data analysis

In order to have a clear understanding of research findings, data analysis was done using SPSS statistical package for windows, version 10 (SPSS, Chicago Illinois, USA). During analysis, Pearson's correlation coefficient was used to test for the association between BMI and CD4 count. The level of significance was set at $p \leq 0.05$. Frequencies were calculated and lastly, for trends, Microsoft Excel package was used to show tables, figures and charts.

3.9. Ethical considerations

Written permission to access and use patients' case notes was obtained from the Directors of Mzuzu Central Hospital and Taiwan Medical Mission to Malawi (Appendix 3 and 4). The study was approved by the College of Medicine Research and Ethics Committee (COMREC).

3.10 Limitations of the study

This was a retrospective study of patient's case notes kept in a busy clinic providing ART. The clinic was never set up to answer questions raised in the study. However the study has managed to glean some useful information from the set of data that was being kept in this clinic. Some of the limitations of this review of case notes include the following:

3.10.1. Small numbers of patients in stages 1 and 2.

There were small numbers of patients in WHO stage 1 and 2. What we did not have is the numbers from these early stages that did not start ART and the reasons why they did not start treatment. Furthermore it is not clear why patients in WHO stages 1 and 2 with CD4 cell count above 250 cells/ mm^3 were started on therapy when the national ART recommendations clearly stipulate that patients in this group without opportunistic infections which classifies them into WHO stages 3 and 4 should not start therapy. Again, due to low numbers of patients in WHO stage 1 and 2, data was not available to identify those patients who had a CD4 count greater than 250 cells/ mm^3 which would have assisted in calculating sensitivity and specificity of staging using CD4 count as gold standard.

3.10.2. WHO staging

There are always issues in determining the WHO stage of patients presenting to health facilities. An audit of W.H.O clinical staging by nurses and clinical officers from health centers within Blantyre versus clinical officers and nurses from Queen Elizabeth central hospital (QECH) showed major differences between the WHO stage recorded by other health center staff and those recorded by QECH staff. It is therefore assumed that possibly clinicians at the Rainbow Clinic in Mzuzu could have as well mis-staged some of the patients prior to initiating them on ART.

3.10.3. Missing data

Some case notes did not have complete data especially at 12 month visits. CD4 cell counts values were the most affected this was at a time when the FACS count machine for CD4 cell count had broken down.

3.10.4. Generalizability

Findings from the study may not be generalized to other settings like the rural areas since this study was only confined to a special group of patients attending the ARV clinic at Mzuzu central hospital a clinic situated in the urban setting as well as being a referral hospital for the Northern region.

In spite of these limitations, it is hoped that the study will offer some insights into the issues regarding initiation and monitoring of ART in HIV positive patients despite the current resource constraints.

CHAPTER 4

RESULTS

4.1. SOCIO-DEMOGRAPHIC CHARACTERISTICS

Out of the 230 patients files chosen for the study, 150 (65%) were females while 80 (35%) were males.

For the whole sample under study, the median age was 37 years (range 2 to 69 years). Looking at females only, the median age was 36 years (range 2 to 64 years) while as for males the median age was 39 years (range 6 to 69 years).

Further findings showed that the largest group of patients belonged to those in age group 30-39 years making up 36%, followed by patients in the age group 40 to 49 years at 27% the lowest group 2.6% was for patients in the age group of 60 to 69 years (Figure 1).

For occupation, 33% of ART recipients were house wives, 23% was for business men and women while the lowest group 1% was for soldiers (Appendix 3).

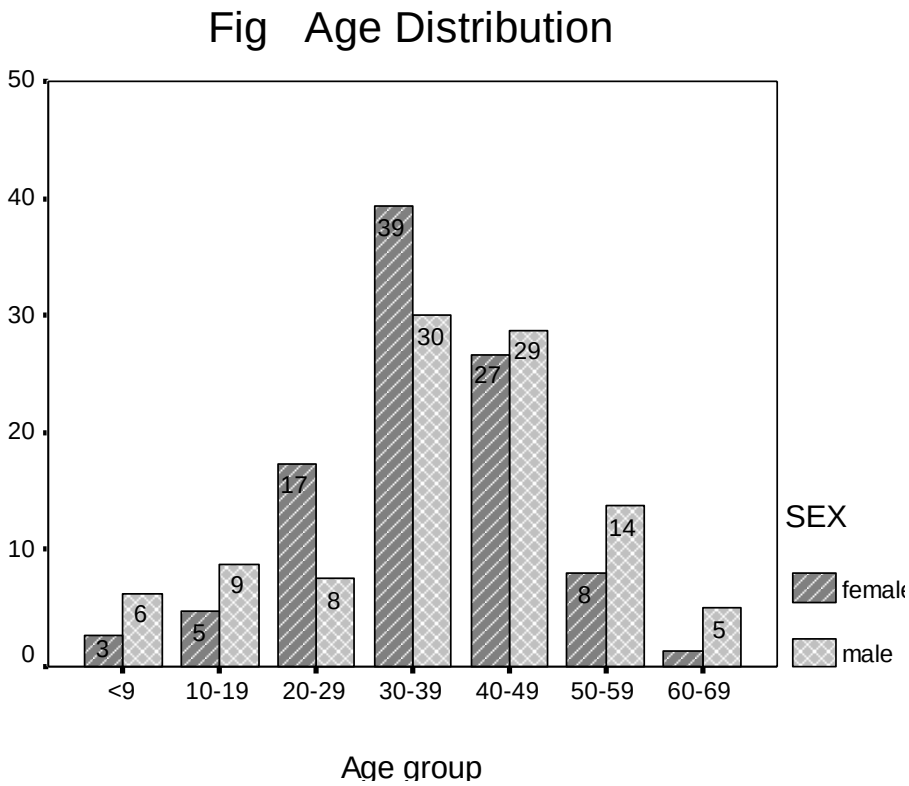

Figure 1: Chart showing age stratified by sex

4.2. WHO clinical staging

Sixty seven percent of patients were in WHO clinical stage 3, 21%, were in WHO stage 4 while the remaining 12% were in WHO stages 1 and 2 (Table 1).

Table: 1. Showing W.H.O clinical staging.

Category	Number	Percentage
WHO stage I and II	29	12
WHO stage III	154	67
WHO stage IV	47	21
TOTALS	**230**	**100**

4.3. WHO clinical staging in relation to CD4 cell counts

Out of 29 patients in WHO stage 1 and 2, 25 had a CD4 count less than 250cells /mm^3 while 4 had CD4 count greater than 250 cells /mm^3. For patients in WHO stage 3, out of 154 patients, 120 had a CD4 count less than 250 cells /mm^3, 34 had a CD4 count greater than 250 cells /mm^3 and lastly, for a total of 47 patients in WHO stage 4, 42 had a CD4 count less than 250 cells /mm^3 while 5 greater than 250 cells/ mm^3 (Table 2).

The initial mean CD4 count values for all 230 patients receiving ART was at 173.5 cells /mm^3 and a standard deviation of 209.5

Other findings derived from calculating the mean CD4 counts amongst patients starting ART in WHO stage 1 and 2 showed that they had a mean CD4 count of 152 cells /mm^3, a 95% Confidence Interval (CI) of 105.1 lower limit and 199.6 upper limit, while as for those patients in W.H.O stage 3 had a mean CD4 cell count of 188 cells/ mm^3, a 95% CI of 155.7 lower limit and 225 upper limit. Lastly, for those patients in WHO stage 4, initial mean CD4 cell count was 140 cells/ mm^3, a 95% CI of 87.7 lower limit and 192 upper

limit (Figure 2). Overall, using t test, findings reveal a significant difference in the CD4 count across all the stages p value less than 0.05.

Table 2: WHO clinical staging and CD4 count values

WHO staging	**CD4 count < 250 cells/ mm^3**	**CD4 count > 250 cells/ mm^3**	**Total patients**
	n (%)	**n (%)**	**n (%)**
I and II	25 (86)	04 (14)	29 (100)
III	120 (78)	34 (22)	154 (100)
IV	42 (89)	05 (11)	47 (100)
TOTALS	**187 (81)**	**43 (19)**	**230 (100)**

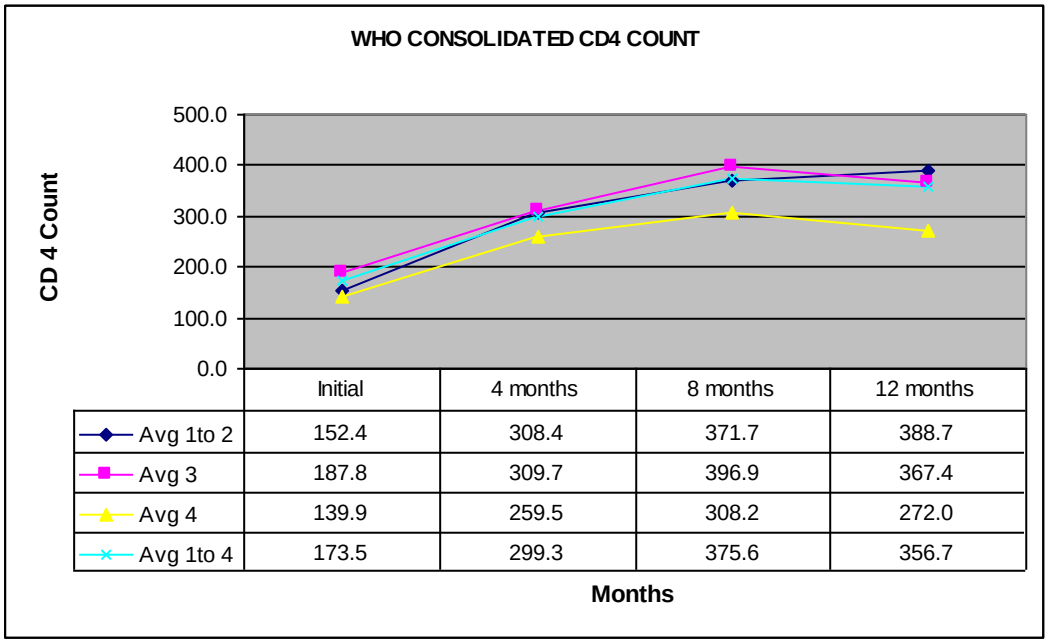

Fig 2: Showing average CD4 count values in the various WHO stages from initiation of ART, every 4 months up to 12 months.

4.4. WHO staging in relation to BMI

Findings show that for all patients in the study receiving ART, their median height was 157cm (range 72cm to 180 cm) median weight was 50 Kg (range 8 kg to 100 kg). More findings reveal that at the start of ART, patients in WHO stage 1 and 2 had a mean BMI of 21 Kg/m^2, 95% CI at 20.4 lower and 24.7 upper limits. While as patients in WHO stage 3 had a mean BMI of 19.7 Kg/m^2, 95% CI of 19 lower 20 upper limits and lastly, for patients in WHO stage 4 their mean BMI was at 20.Kg/m^2, 95% CI 19, lower and 21.5 upper limits. Overall, for all patients in the sample in WHO stages 1 to 4, initial mean BMI was 20.Kg/m^2, 95% CI 19.7 lower limit and 20.8 upper limits, at 4 months mean BMI was 22.Kg/m^2, 95% CI 21.5 lower limit and 22.6 upper limits. Finally, at 12 months follow up, mean BMI was 22.4.Kg/m^2 95% CI of 22.3 lower limit and 23.4 upper limits. Overall looking at individual WHO stages findings reveal that at 12 months of follow up, patients receiving ART in WHO stage 4 had a higher improvement in their mean BMI from an initial value of 20.3 kg/m^2, 95% CI of 19 lower to 21.5 upper and a rise of up to 23.3 kg/m^2 and a 95% CI of 21.9 to 24.6 while as patients receiving ART in WHO stage 1 and 2 had the least BMI improvement from 21 kg/m^2 to 22 kg/m^2, 95% CI of 21.9 to 26.5 (Figure 3). Using t test, results show that findings were statistically significant p value less than 0.05.

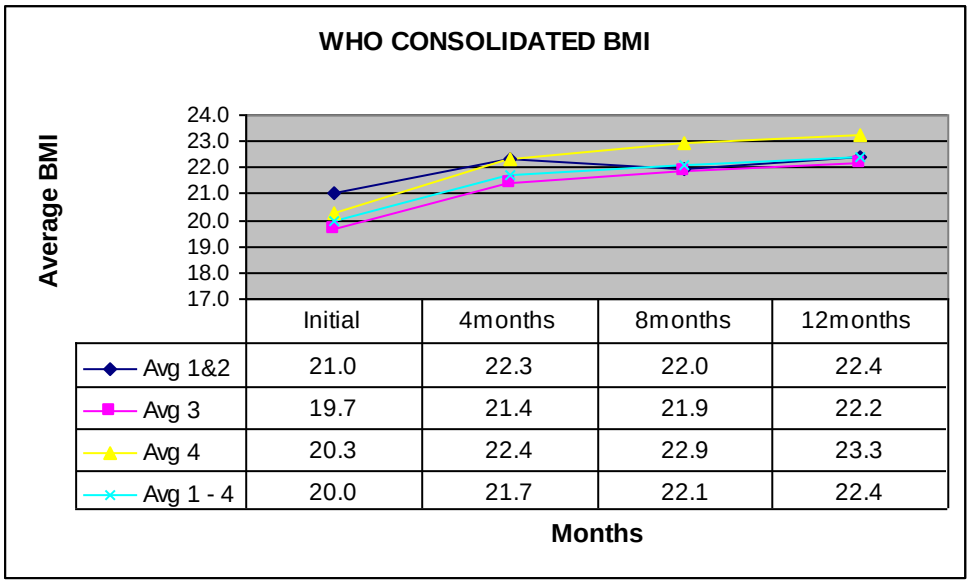

Fig 3: Showing Average BMI values from initiation of ART every 4 months up to 12 months

4.5. Relationship between BMI and CD4 count

Table 3: Coefficient values for initial CD4 count

Table 3: Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	271.772	71.937		3.778	.000	130.002	413.542
	INITIAL BMI	-4.766	3.476	-.092	-1.371	.172	-11.617	2.085

a. Dependent Variable: FIRST CD4 COUNT

Where $\hat{Y}=\alpha + ßX$ where α is a constant, ß is a slope of the regression line, $\hat{Y}$ is the estimated initial CD4 Count and X is initial BMI. Regression Model is given from the Table above $\hat{Y}=271.772 - 4.766$ (Initial BMI). To test

whether there is a linear association between initial CD4 count and the initial BMI the following hypothesis testing has been used;

$H_0 : \beta = 0$ Vs. $H_1 : \beta \neq 0$ $\alpha = 0.05$ (p-value; level of significant)

Null Hypothesis will be rejected if p-value calculated is less than 0.05. From the Table 3 above, p-value = 0.172 which is greater than 0.05. Hence there is not enough evidence to reject the null hypothesis i.e. β is not significant. One concludes that there is no linear association between initial CD4 count and initial BMI this means that initial BMI does not have an effect on the initial CD4 Count.

Table 4: Coefficient values for fourth CD4 count at 12th month

Table 4: Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	323.969	107.964		3.001	.003	110.477	537.460
	BMI 12 MONTHS	-5.762	4.664	-.105	-1.24	.219	-14.984	3.461

a. Dependent Variable: FORTH CD4 COUNT

the estimated CD4 count at 12 month and X is the BMI at 12 month. Regression Model is given by $\hat{Y}=\alpha + ßX$ from the Table 4 above. Where α is a constant, ß is a slope of the regression line, $\hat{Y}$ is the estimated 12^{th} month CD4 count and X is 12^{th} month BMI. Regression Model is given by

$\hat{Y}$=323.969 – 5.762 (12-month BMI). To test whether there is a linear association between the 12th month CD4 count and the 12th month BMI the following hypothesis is tested;

$H_0 : \beta = 0$ Vs. $H_1 : \beta \neq 0$ α = 0.05 (p-value; level of significant)

Null Hypothesis will be rejected if p-value calculated is less than 0.05. From the Table 4 above, p-value = 0.219 hence there is not enough evidence to reject the null hypothesis. This means that there is no linear association between CD4 count and BMI at 12 months.

4.6. Patient outcome by twelve months of ART

One hundred eighty seven (81%) patients were alive, twenty seven (12%) patients, had transferred out, four (2%), were defaulters of treatment while as twelve (5%) had died during one year period of ART use (Figure 4)

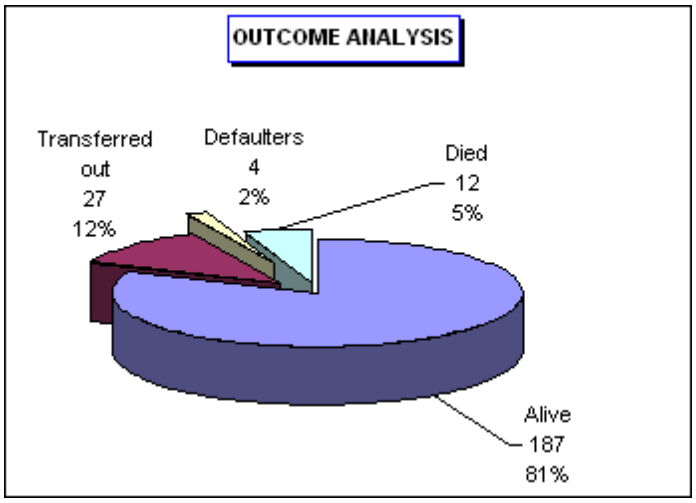

Figure 4: Outcome by the characteristics of study participants

4.7. Deaths analysis

A further observations of the deaths revealed that of the twelve patients (5%) who died, 7 (58%) were males and 5 (42%) were females. For all patients who died, 8 were in WHO stage 3, while 4 patients were in WHO stage 4. More findings showed that in all quarters some patients died the numbers were as follows: 2 patients died during the first 3 months, 2 patients in the second quarter while 3 in the third quarter and the remaining 5 patients died during the fourth quarter. Laboratory findings show that patients who died had a lower mean CD4 cell count at initiation of treatment and had a poorer mean CD4 count at follow up (102 cells/ mm^3) as compared to the other group of patients who showed a slightly higher mean CD4 count of 133cells/ mm^3 at initial and 323 cells/ mm^3 at 12 months follow up of ART.

As for BMI values, the overall picture showed that for the patients who died, their mean BMI values were unchanged at initial and follow up of period (20.7 Kg/m^2 and 20.6 Kg/m^2).

Furthermore, using Kaplan Meir survival curve (Figure 5) the graph shows a straight line for stage 1 and 2 which confirms that there were no deaths in this group, however, there is a slight drop in the graph for patients in stage 3 and 4, which shows that there were some deaths in this group. Overall, statistically, there were no differences in the survival rates amongst patients taking ART in all the WHO stages.

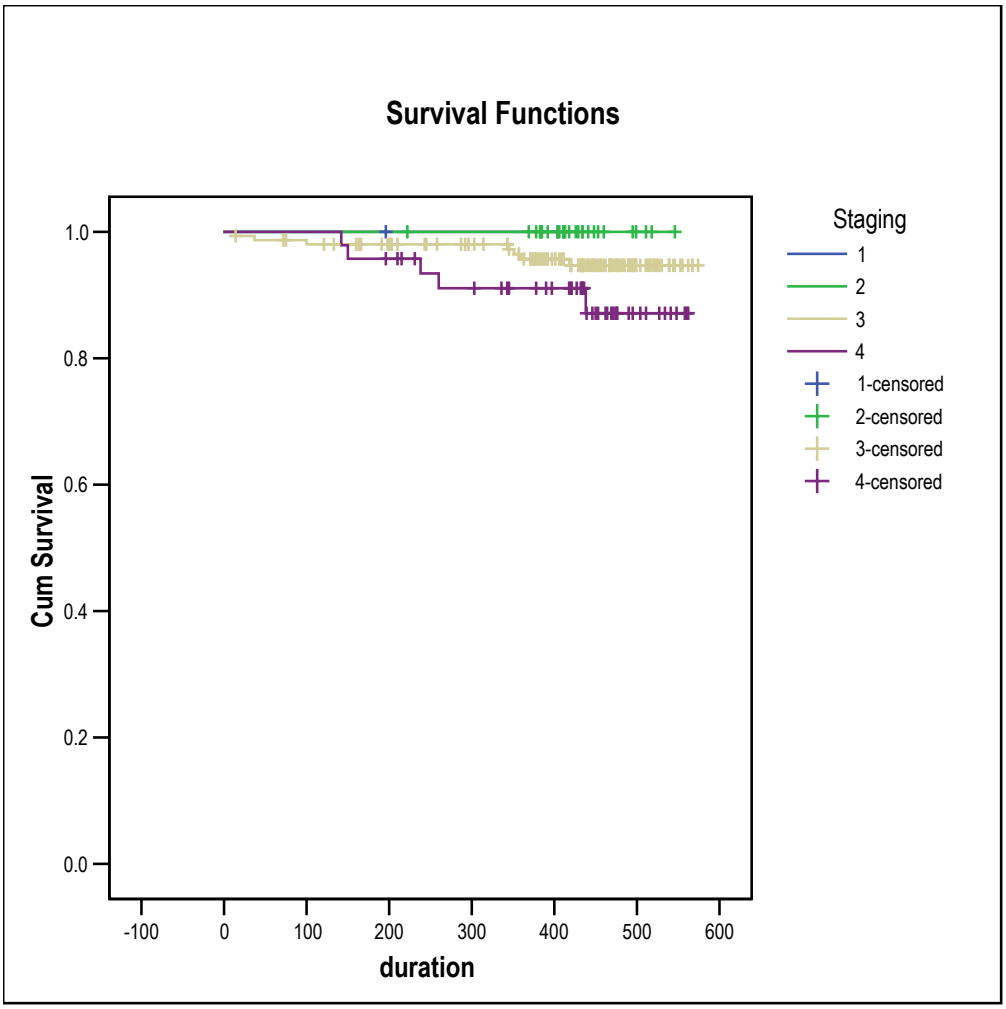

Fig 5: Cummulative survival rates among patients taking ART

CHAPTER 5

DISCUSSION

Sub-Saharan Africa remains the world's worst affected region by the HIV/AIDS epidemic (UNAIDS report 2004). Malawi is one of the countries in Sub-Saharan Africa at the epicenter of this epidemic with over 180,000 patients requiring therapy as of the end of 2006 (NAC, 2005). For a government faced with this huge challenge of providing ART with a small resource base, it is imperative that methods of rationing care should be adopted. However, these methods of rationing therapy are expected to be fair. The national ART program decided to use a public health approach in providing ART. The programme chose the route of low technology to support and serve a large number of patients. Questions however remain as to whether this approach is serving many Malawians in need of ART well. In this study we have also looked at the effect of using WHO staging as a sole entry criterion and compared it with using CD4 count in combination with other parameters. The discussion of the results is now being done under the following headings:

5.1. Demographic characteristics

Findings from the study revealed that for patients accessing ART at the Rainbow clinic, women out number men by a ratio of 2:1. This is what is expected if provision of ART services in Malawi was equitable since women bear the brunt of the HIV epidemic in the Sub-Saharan Africa. The higher

percentage of HIV infection amongst females is similar to the overall findings of Malawi national figure which also shows that by December 2006, out of 81,821 cases on ART, 61% were females. Again, figures from other SADC countries reveal that almost 60% of all HIV-1 infection in this region is found in women (UNAIDS 2004). Nguyen (2006) reports that in Sub Saharan Africa, among HIV infected people aged 15 to 24 years, 76% are women. Furthermore, the findings also confirm how HIV is affecting the most productive group in the country.

The biggest group accessing ART at the Rainbow clinic is in the 30-39 year age range. Considering that progression from HIV to AIDS takes about 8 to 10 years in Africa, one would assume that these women would have contracted HIV in their teens while some were in their twenties. These findings further confirms the MDHS and UNAIDS (2005) reports that states that young women in Malawi are almost twice to three times likely to be infected with HIV as compared with young men this is because due to poverty, some parents encourage their girl child to engage in transaction sex (NAC, 2003) and some women depend mainly on sex for their livelihood this makes them prone to many sex partners rendering them to be at high risk of HIV infection (Geubbels 2006). Hence this scenario and other factors in general place a higher HIV prevalence among women in Malawi than in men. By the year 2004, 13% of all women in the country were living with HIV/AIDS compared with 10% of men (MDHS 2004) this is a major shift in

the epidemic when more men were infected in the early days of the HIV/AIDS epidemic. Some of the reasons advanced for women being more affected include the following:

1. The prevalence in women may not be higher than in men but women may have more avenues for HIV testing compared with men. HIV surveillance in Malawi started with antenatal mothers and as such more women in Malawi are tested for HIV compared with men. However more men patronize MACRO-VCT services compared with women. At these centers the few women that test for HIV show higher incidence rates compared with men.
2. Women may be at higher risk because of gender violence and social inequalities. Vulga et al (2001) states that vulnerability to HIV is heavily influenced by socio cultural factors and societal norms particularly gender and sexuality
3. Some cultural traditions such as male dominance and older men's preference for young women reflect power imbalance and limits women's inability to refuse or negotiate or control sexual interaction. This mainly result into unprotected sex (Lamptey, 2006) and hence at high risk of HIV infection.

5.2. WHO staging and CD4 count

Results show that for patients accessing ART at the Rainbow Clinic, using the WHO staging alone would not assist much in deciding which patients had been severely immunodepressed considering that the final progression to AIDS is characterised by very low CD4 counts and a rise in viral load and a low BMI does not necessarily mean severe immunological depression. Although patients in WHO stage 3 did show some increase in the mean CD4 count during the 4th and 8th month's period, as compared to patients in WHO stage 4, overall, the mean CD4 count was not very different from the mean CD4 cells counts of patients in stages 1&2 and 3 respectively). An explanation on the variation of the mean CD4 count for WHO stage 3 being higher than WHO stage 1 and 2 could be because patients in WHO stage 1 and 2 need to have a CD4 cell count less than 250 cells/ mm^3 or else they cannot start ART but patients in stage 3 or 4, can start ART based on their clinical condition irrespective of the CD4 cell count (NAC/MOH, 2006). Secondly, some HIV positive patients with opportunistic conditions like pulmonary TB and Kaposi's sarcoma (KS) is common in WHO stage 3 and 4 patients and these conditions can at the same time have CD4 lymphocyte counts greater than 250 cells/ mm^3 hence showing a raised mean CD4 count for WHO stage 3 patients. A search of Medline has not provided us with enough information on studies that have been done to compare WHO staging with the level of immunodepression in terms of CD4 cell count.

MacLennan (2007), states that clinical events do not fully predict immunological status hence this statement is inline with findings from the study which demonstrated that 12% of patients in WHO stage 1 and 2 would not have started ART if the clinic was using WHO clinical staging only. Again, more patients (19%) would not have started ART if the criterion was solely based on using CD4 cell count considering that these patients were having a CD4 cell count greater than 250 cells/mm^3 on initial ART. It is therefore suggested on the need to consider if both systems of WHO clinical staging and CD4 count could be used to allow for more patients to access ART services and improve their quality of life in line with WHO (2002) recommendation on the use of simple clinical criteria to stage HIV infection in association with low cost laboratory tests.

Overall, patients in this Rainbow clinic showed some improvement in CD4 cell count over the 12 months of audit. However, specifically, In terms of improvement of CD4 cell count over time, patients in WHO stage 1 and 2 and those in WHO stage 3 had better trajectory of their mean CD4 cell count compared to patients in WHO stage 4. Gallants (2003), states that there are factors that influence CD4 cell counts which include, seasonal and diurnal variations, corticosteroids and some intercurrent illnesses. However, He explains further that in general, CD4 cell count typically is expected to rise by about 50 cells/mm^3 at 4 to 8 weeks after viral suppression with ART and then increases an additional 50-100 cells/mm^3 per year thereafter. Finally,

Gallants (2003) concludes that at times there may be an initial delay in CD4 count response that cannot be explained furthermore, CD4 cell count usually declines rapidly up to 100-150 cells/mm^3 in 3 to 4 months when therapy is discontinued. Highleyman (2003) also states that many factors can affect the CD4cell count these include stress, one's menstrual cycle, stress and time of the day. She further explains that without treatment, CD4 count decrease usually by 30 to 100 cells cells/mm^3 per year.

5.3 WHO staging and BMI

BMI is the weight in Kilograms divided by height in squared meters and it is used to assess individuals' obesity or thinness. The cut off point of 18.5 Kg/m^2 is used to define chronic energy deficiency (MDHS, 2004). Protein energy malnutrition compromises all aspects of immune system; cell medicated immunity and antibody production. When malnutrition and HIV occur together, the immune compromise is compounded as the two conditions synergistically work together to make the individual more susceptible to infection and make the infection that occur become more severe (UNICEF, 2003).

Weight loss has been shown to be one of the criteria included in clinical assessment of HIV infected patients in order to determine ones WHO clinical stage, disease stability and or progression (Crowe, 2003).

Results from the study show that with time, all patients showed improvement in their mean BMI values from baseline as evidenced by findings which showed that those patients starting ART in WHO stage 4 had the highest improvement in their mean BMI at 15.3% while as patients in WHO stage 1 and 2 showed the least mean BMI improvement at 6.7%. This is somehow expected since most patients in WHO clinical stages 1 and 2 would not be wasted to begin with.

5.4. BMI and CD4 count

HIV infected patient's nutritional status and BMI decrease as their immune system becomes compromised. One of the ways in measuring immune function is by checking the CD4 lymphocyte count. Unfortunately, results from the study show some variations in CD4 counts in patients with the same WHO clinical stage condition. The study then did attempt to find out if at all there was some relationship between CD4 count and BMI count at initial treatment and at 12 months follow up. From the results shown (Table 3 and 4), one could concludes that there is no linear association between CD4 count and BMI at initial p value 0.172 and 12 months of ART p value 0.219 with a level of significance p value at 0.05.

5.5. Death analysis

The study reveals that twelve (5%) patients had died within the 12 months period of ART use. This is lower compared to the National figure which

states that by December 2006, 11% of patients on ART had died. All these patients were in WHO stages 3 and 4 slightly higher than the national figures of 65% for stage 3 and 23% for stage 4. Other findings from a study conducted by Hosseinipour (2003), states that during the first year of ART implementation in Malawi, mortality rate was high among patients who start therapy with a very low CD4 counts however drug tolerance was high. However, as for BMI values, the overall picture showed that for the patients who died, their mean BMI values were unchanged within the study period.

These findings may suggest that immunodepression could be a more important prognostic marker compared to wasting.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

This audit has demonstrated that there may be disparities between the uses of W.H.O clinical staging as the only method of recruiting patients to the ART than using CD4 cell count. Since the study used a retrospective approach, it is proposed therefore that a prospective study be conducted in which a direct comparison between the uses of CD4 cell count and WHO staging as entry criteria for patients starting ART.

6.2. Recommendations

With all the study findings and discussions above, the following recommendations are made;

- There is need for policy makers in poor resource setting like Malawi Ministry of Health need to consider and advocate for adopting affordable, simple and cost effective laboratory facilities for CD4count check to be included as an integral part of the diagnostic test before initiating ART in patients who are in W.H.O clinical stage 1 and 2. A simple rapid dip stick similar to HIV test would be best.

- There is need to establish more new sites in the country for provision of CD4 cell counts in order to capture clients of who would be missed for ART if providers only used the clinical guidelines of W.H.O staging criteria.

- There is need to increase availability of Counseling and Testing (CT) services to enable individuals know their HIV status early enough and if positive, the knowledge of their HIV status would allow them to better protect themselves, their partners, plan their future well, access early care, support and ARV therapy.

- There is need to advocate for more strategies to empower young girls with more knowledge and skills to enable them delay their sexual debut, say no to sex, or if need be negotiate for safer sex.

It is hoped that the findings and discussions of this study will add to the existing body of knowledge on HIV and broaden further individuals understanding on issues that concern HIV positive patients receiving antiretroviral therapy.

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APPENDICES

Appendix 1 : Grants table showing the Study Period

	2005 2006								
	Dec 2005	Jan 2006	Feb 06	Mar 06	Apr-May 06	Jun-July 06	Aug-Sept 06	Nov 06	Dec 06
Literature Review									
Proposal Development						`			
Data Collection Tools Development									
Recruiting and Training Field Assistants									
Pre-testing the study tools									
Piloting									
Data collection									
Data entry									
Data Analysis									
Report Writing									
Dissemination of Findings									

Appendix 2

CHECKLIST FOR MONITORING BODY MASS INDEX AND CD4 COUNT

ID NO.	SEX	AGE	Occupation	HT	WT	INITIAL JAN–JUNE 2005		4 MONTHS JULY–OCT 05		8 MONTHS NOV 05–FEB 06		12 MONTHS MAR 06–JUN 06		OUTCOME
						BMI	CD4 COUNT	BMI	CD4 COUNT	BMI	CD4 COUNT	BMI	CD4 COUNT	

Appendix 3:

TABLE 5: AGE GROUP * OCCUPATION * SEX CROSS TABULATION

SEX	AGE GROUP	OCCUPATION								Total
		Business	Farmer	Health worker	Housewife	Other	Soldier/ Police	Student	Teacher	TOTAL
Female	<9					1		3		4
						25.0%		75.0%		100.0%
	10-19							7		7
								100.0%		100.0%
	20-29	8			13	4			1	26
		30.8%			50.0%	15.4%			3.8%	100.0%
	30-39	14	1	3	30	8			3	59
		23.7%	1.7%	5.1%	50.8%	13.6%			5.1%	100.0%
	40-49	10	2		21	4	1		2	40
		25.0%	5.0%		52.5%	10.0%	2.5%		5.0%	100.0%
	50-59				10	2				12
					83.3%	16.7%				100.0%
	60-69				1	1				2
					50.0%	50.0%				100.0%
	Total	32	3	3	75	20	1	10	6	150
		21.3%	2.0%	2.0%	50.0%	13.3%	.7%	6.7%	4.0%	100.0%
Male	<9					1		4		5
						20.0%		80.0%		100.0%
	10-19							7		7
								100.0		100.0%

							%		
20-29	3				3				6
	50.0%				50.0%				100.0%
30-39	9			1	12			2	24
	37.5%			4.2%	50.0%			8.3%	100.0%
40-49	9	4	3		4	1		2	23
	39.1%	17.4%	13.0%		17.4%	4.3%		8.7%	100.0%
50-59	1	1			8	1			11
	9.1%	9.1%			72.7%	9.1%			100.0%
60-69		1			2			1	4
		25.0%			50.0%			25.0%	100.0%
Total	22	6	3	1	30	2	11	5	80
	27.5%	7.5%	3.8%	1.3%	37.5%	2.5%	13.8%	6.3%	100.0%

Appendix 4

Mzuzu Central Hospital
P/Bag 209
Luwinga
MZUZU 2.

28th December 2005

The Medical Director
Taiwan Medical Mission
P/Bag 2010
Luwinga
Mzuzu 2

Dear Sir,

REQUEST FOR CLEARANCE TO CONDUCT A RESEARCH STUDY

I write to request for permission to conduct a study at Mzuzu Central Hospital Rainbow Clinic in partial fulfillment of a Masters Degree in Public Health.

I am a student currently studying with College of Medicine in Blantyre. The study is entitled "Correlation between changes in Body mass index and CD4 count in HIV Positive patients on Antiretroviral therapy". The intention is to extract data from patients files using a checklist on sex, age, height, weight, Body mass index, temperature, CD4 count on initial visit then quarterly basis for a period of one year.

Looking forward to your favourable response.

Yours faithfully,

T.N. Soko (Mrs)
PRINCIPAL INVESTIGATOR

Appendix 5

TAIWAN MEDICAL MISSION

P/Bag 2010, Luwinga, Mzuzu 2
Tel: 01 333 911 Ext. 2103
Fax: 01 333 152 / 01 334 384
E-mail:cmsmtw@yahoo.com
cmsm@malawi.net

January 18, 2006

Mrs. T.N Soko
Mzuzu Central Hospital
Luwinga
Mzuzu 2

Dear Mrs. Soko,

RE: REQUEST FOR CLEARANCE TO CONDUCT A RESEARCH STUDY

Reference is hereby given to your letter dated December 28, 2005, in which you requested to conduct a study entitled "Correlation between changes in Body Mass index and CD4 count in HIV positive patients on Antiretroviral therapy" at the Mzuzu Central Hospital Rainbow ARV Clinic in fulfillment of a Masters Degree in Public Health.

I am pleased to inform you that have you the permission to conduct the said study at the Rainbow ARV clinic as soon as it may be convenient to you.

I wish you every success in your study.

Yours Sincerely,

Thom Phalula
For the Director, Taiwan Medical Mission to Malawi.

Appendix 6

Tel.: (265) 1 334216/(265)9941120
Fax: (265) 1 334 270
E-mail: directormch@malawi.net

Address all your correspondence to:

THE DIRECTOR
MZUZU CENTRAL HOSPITAL
PRIVATE BAG 209
LUWINGA
MZUZU 2

10th January 2006

Attention: Mrs T.N. Soko

Dear Madam

PERMISSION TO CONDUCT A RESEARCH STUDY

With reference to your letter dated 28th December 2005 requesting to conduct a study at rainbow Clinic on "correlation between Changes in Body Mass index and CD4 Count in HIV positive patients on Antiretroviral Therapy."

I would like to inform you that I have no objection for you to conduct the said study. You are therefore asked to report to the in-charge of the Rainbow Clinic for necessary arrangements for this important activity.

Dr. P.S. Juma

pp Dr H. Juma
Hospital Director

Appendix 7 Study Budget

3 Reams photocopying paper	@ K700.00 each	K2, 100.00
1 Ream ruled paper	@ K500.00 each	K500.00
3 Floppy diskettes	@ K200.00 each	K600.00
5 Black/ Blue Pens	@ K40.00 each	K200.00
5 Pencils	@ K20.00 each	K100.00
3 Erasers	@ K100.00 each	K300.00
10 envelops	@ K 20.00 each	K200.00
1 memory stick	@ K20,000.00	K20,000.00
ALLOWANCES		
1 Research Assistant		K10, 000.00
1 Statistician		K8, 000.00
Secretarial Services		K5, 000.00
Photocopying Services 500 copies	@ K6.00 each	K3, 000.00
ADMINISTRATIVE COSTS		
Communication		K8, 000.00
Meals and Refreshments		K7, 000.00
Transport		K20, 000.00
Binding of thesis		K5, 000.00
Dissemination		K10, 000.00
TOTAL COST		K100, 000.00