UTILITY OF AN ALGORITHM OF SURROGATE MARKERS FOR CD4 COUNT TO DETERMINE ELIGIBILITY FOR HAART AMONG HIV INFECTED PREGNANT WOMEN.

A dissertation submitted to the University of Nairobi, in partial fulfilment of the requirements, for the award of the degree of Master of Medicine in Obstetrics and Gynaecology

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DECEMBER 2010

DECLARATION

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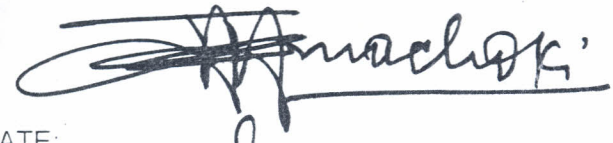

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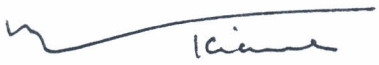

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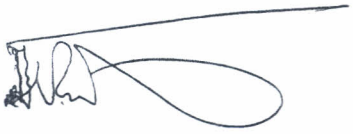
SIGNATURE: 

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DEDICATION

This work is dedicated to all HIV positive women who desire motherhood and would like to protect their babies from HIV infection.

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ABBREVIATIONS

ADI	AIDS defining illness
AMPATH	Academic Model of prevention and treatment of HIV
AMRS	AMPATH Medical Record System
ANC	Antenatal Clinic
ART	Anti-Retroviral Therapy
ARV	Anti-Retroviral Drugs
AUC	Area under the Curve
BMI	Body Mass Index
CD	Cluster of differentiation
CI	Confidence Interval
ELISA	Enzyme-Linked immunosorbent assay
HAART	Highly Active Antiretroviral Therapy
HB	Haemoglobin level
HIV	Human Immunodeficiency Virus
J	Youden's Index
KAIS	Kenya AIDS Indicator Survey
MTCT	Mother to child Transmission
MUAC	Mid-Upper Arm Circumference
NASCOP	National AIDS/STI Control Programme
NGO	Non-Governmental Organisation

NPV	Negative predictive value
OI	Opportunistic Infections
PMTCT	Prevention of mother to child transmission
PPV	Positive Predictive Value
RH	Relative Hazard
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristics Curves
TB	Tuberculosis
TLC	Total Lymphocyte count
UNGASS	United Nations General Assembly Special Session
WCS	WHO Clinical Staging
WHO	World Health Organisation

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ABSTRACT

Background: CD4 count is an important marker of disease progression in patients with HIV. But CD4 count testing is not always readily available in developing countries like Kenya. Studies have shown significant correlation between CD4 count and Total Lymphocyte Count (TLC) including two studies done in Kenya among children and non-pregnant adults. Various TLC cut-offs including WHO TLC cut-off of 1200 have had low predictive value for indentifying subjects with low CD4 count. Both WHO and Kenya PMTCT programme recommends HAART for CD4 count <350cell/mm^3.There was need therefore to revise the TLC cut-off for CD4 Count <350cell/mm^3 and develop clinical algorithms using biomarkers like haemoglobin level and BMI to raise the predictive value of TLC.

Methods and Data analysis: This was a retrospective analysis of cross-sectional data from HIV infected pregnant, ARV naive women. Data was extracted from patients' charts and entered into a data proforma. The relationship between CD4 and TLC, BMI, HB and WHO Clinical Stage (WCS) was calculated using Pearson's Correlation and linear regression. Two by two tables were constructed to determine performance of various TLC thresholds using the Sensitivity, Specificity, PPV and NPV. These were used to compute Receiver Operating Curves (ROC) to determine the predictive accuracy for each of the biomarkers singly and in various combinations. Data was be analysed by SPSS version 15 and Stata 10.

Results: Of 362 HIV positive pregnant women, 160(44.5%) had CD4 count <350 cells/mm^3. Using linear regression optimal cut-off points for TLC, HB, BMI were 850cell/mm^3, 8.4g/dl and 15.5kg/m^2 respectively. These cut-off points were highly specific but with very low sensitivity. The best cut-off point using generated sensitivity and specificity values was TLC≤2200 with Sensitivity of 68% and Specificity of 51%. A 3-step algorithm of WCS II&III, TLC≤1000 and HB≤12g/dl; in that order was the most optimal with a Sensitivity, Specificity, PPV, NPV , Youden's index(J) and ROC AUC of 86.21%, 92.00%, 94.3%, 74.20%, 78.00% and 89% respectively.

Conclusion: TLC, HB, WCS and BMI have low predictive accuracy for CD4 count <350cell/mm^3 when used alone. Our data suggests that HB, BMI, and WCS increased the Sensitivity of TLC at all thresholds. These markers combined in an algorithm are useful surrogate markers for CD4 Count and can be used in resource poor settings to determine eligibility for HAART.

INTRODUCTION

1.1 Background Information

Estimates from UNAIDS indicate a total of 33.4 million people living with AIDS with an estimated 2.7 million new infections occurring in 2008. Sub-Saharan Africa remains the most heavily affected region, accounting for 71% of all new HIV infections in 2008. [59] The rapid scaling-up of antiretroviral therapy in sub-Saharan Africa has generated considerable public health gains. As of December 2008, 44% of adults and children (nearly 3 million people) in need of antiretroviral therapy in the region were estimated to be receiving such services. Treatment scale-up is having a profound effect on HIV-related mortality in many countries. In Kenya, AIDS-related deaths have fallen by 29% since 2002 (NASCOP, 2007). [59]

According to KAIS report an estimated 1.42 million people were HIV-infected by 2007. Of those eligible for ARVs (indicated as CD4 Count ≤250cell/mm^3) only 40.5% were on ARVs. Kenya national HIV prevalence is estimated at 7.1% while the HIV prevalence among pregnant mothers is 9% with 53,000 children per year infected with HIV. According to UGASS 2010 Country progress report, about 58,591 HIV positive pregnant women received antiretroviral prophylaxis to reduce the risk of mother-to-child transmission of HIV in 2009. It is estimated that there were 81,000 HIV positive women in need of PMTCT services, giving coverage of 72.32 percent for HIV positive pregnant women who received antiretroviral prophylaxis to reduce risk of MTCT. Scaling-up efforts for PMTCT are being made through NASCOP as uptake of testing and counselling increases. [60]

Despite intensive efforts to scale-up treatment, reduction of prices through generic ARVs, access to treatment in Kenya and indeed in sub-Saharan region is far from universal where the disease burden is still enormous. [9] The cost of diagnostics in determining eligibility and monitoring for HAART remain an obstacle to access to ART. The WHO in recognition of this fact proposed a public health approach with treatment guidelines intended to support and facilitate the proper management and scale-up of ART. The aim is to provide standardized and simplified ARV regimens and ensuring that ARV programmes are based on scientific evidence to avoid substandard protocols that compromise the outcomes of treatment and ensure efficient implementation. [9]

The WHO recommends starting HAART in those patients with WCS IV disease irrespective of the CD4 count and in those with WHO Clinical stages II or III disease with TLC of ≤1200 cells/mm^3, where CD4 lymphocyte count is unavailable.[2] It is also recommended that any pregnant woman with a CD4 count below 350 cells/mm^3 and WHO clinical stage III disease should initiate ART. [44] These guidelines were developed from evidence generated from clinical trials from North America, Europe and Australia and observational studies in resource limited settings. The influence of geographical location, racial and ethnic background, age, sex and conditions of living, on the distribution of human peripheral blood T-lymphocyte subpopulations is documented in various studies. Generalisation of the findings should therefore be done with caution. [2][53]

Few studies assessing the relationship between CD4 count and Total Lymphocyte Counts have been done in sub-Saharan. These studies have shown significant correlation between TLC and CD4 counts. However the sensitivity and specificity of TLC as a marker of levels of CD4 count remain low making TLC an imperfect predictor of CD4 count. Other studies have assessed different biomarkers such as Erythrocyte Sedimentation Rate, C-reactive protein, HB, BMI and WCS. These have been assessed singly or in different combination with other markers usually TLC either as predictors of other surrogates like CD4 count or predictors of a clinical outcome like ADI or death. This makes it difficult for meaningful comparison to be made. However evidences indicate that HB and BMI are strong independent markers of HIV disease progression and mortality. [2][21][26][29][35][46]

In addition to the cost of ARVs, the cost of diagnostics is one of the challenges hampering response to the HIV pandemic in sub-Saharan Africa and in particular Kenya. Data from the Logistic Management Unit Database for NASCOP (2009) showed that there were 129 CD4 count machines; more than half of these are in private institutions. There is need for affordable and reliable markers for initiating and monitoring HAART among HIV patients. Extra Laboratory services cost can be channelled to acquiring more ARV's and improving the health care infrastructure.

CD4 is a gold standard test in determining those eligible for HAART as well as monitoring treatment in resource rich settings. A good diagnostic test should have both high sensitivity (few false negatives) and specificity(few false positives).The challenge is to determine TLC cut-off for CD4 count of 350cell/mm^3 recommended

for pregnant women and reconcile the competing aims of sensitivity and specificity. Raising the cut-off and use of other biomarkers such as HB and BMI in algorithm does improve the diagnostic accuracy of TLC. [2] In this study relationship between CD4 Count and TLC, HB, BMI and WCS was determined using correlation and linear regression. The predictive accuracy of each of the predictor markers alone and in combination were determined by calculating the area under the ROC curves.

1.2 Literature Review

World Health Organisation has offered leadership through support of individual countries and advocacy to donors culminating in ARV prices reduction and the establishment of Global Fund to fight AIDS. United Nations has committed member governments to providing the highest attainable standard of care including Anti-retroviral treatment for people living with HIV/AIDS. Anti-retroviral treatment is part of an overall essential care package of HIV infected persons and an integral part of HIV prevention programmes. [1] Kenya is no exception and its PMTCT program aims at reducing the proportion of infants infected with HIV by 20% by 2005 and 50% by 2010. [18] According to PMTCT National Guidelines the government hopes to offer comprehensive obstetric care to all antenatal mothers and this includes ART services. [16] No doubt that scaling-up efforts are being made through NASCOP. In 2003, PMTCT services were offered in 463 health facilities; in 2007, PMTCT services were offered in 2000 health facilities; in 2008, PMTCT services were offered in estimated 3000 (60%) health facilities. [56]

Utility of CD4 count as a surrogate for HIV disease progression and specifically in determining eligibility to HAART is unquestionable. In resource rich settings and in standard clinical practice, CD4 count along with clinical indices such as HIV RNA viral load measurement is central to the decision to initiate HAART. CD4 Count is an independent risk factor for progression of HIV disease and death. Brown et al found that the CD4 cell count and the CD4% were most predictive of death. Even HIV-1 viral load did not provide a better predictive value beyond that provided by the CD4 cell count and was a less predictive marker than were the CD4 cell count and CD4% measurements. [21] However in sub-Sahara Africa CD4 Count is not always available and cost is prohibitive because it uses flow cytometry, which require training and expertise.

Diagnostic accuracy of surrogate markers is critical in the management of HIV. The decision to start HAART is an issue of concern to both the physician and patient. It involves making a judgment about when the benefits of therapy outweigh the harms. HAART should be commenced early enough to avoid any clinical consequences of immune suppression and maximise immune reconstitution, but late enough to minimise harms such as drug adverse effects, development of drug resistance, and burdens such as the cost of medication. [19][36] Delaying ART until CD4 count is 200 cell/mm^3 increases mortality and the same is observed in the first year on therapy, with such low CD4 counts at initiation of treatment. [26][46] Brown et al found a 2.1% estimated risk of mortality at 1year postpartum underscored the typically early disease status of HIV-1 infected women during pregnancy when they are not on treatment. [21]

Utility of TLC as surrogate is recognized by WHO and recommends HAART when TLC ≤ 1200 cell/mm^3 where CD4 count is unavailable. Most studies have shown a significant correlation between CD4 count and TLC even in pregnancy and in non-pregnant populations. This correlation is not sufficient enough. The sensitivity and specificity has been found to be low. [2] Many studies have found TLC of 1200 threshold to have poor sensitivity for CD4 count of 200cells/mm^3. [2][6][21] There is need for other thresholds. WHO clinical stage III disease, a CD4 Count threshold < 350 cells/mm^3 has been identified as a level below which functional immune deficiency is present and ART should be considered. This level also conforms to what is indicated in other consensus guideline documents. [44]

One challenge to using TLC for predicting the disease stage is that it does not show a linear decline throughout HIV infection, but rather a period of stability followed by a more rapid decline preceding clinically defined AIDS. Furthermore, TLC like CD4 count can also be affected by a number of factors independent of disease progression. [48] These include steroid use and presence of opportunistic infections. Several studies report that CD4 count remains relatively stable in pregnancy. Toumala et al assessed changes in lymphocyte subsets during pregnancy and one year postpartum in HIV infected women. The study concluded there are no clinically significant changes during pregnancy or postpartum in any lymphocyte parameters (CD4, CD8 and TLC) assessed. [51][54] Other studies indicate that ante partum and postpartum are periods in which Lymphocytes cells could naturally vary. [15][22][24][31][32] Because of these epidemiological influences there are recommendations that data used should be population specific.

A cross-sectional study of HIV-infected adults done in Uganda, evaluated ART-eligibility for WCS I, II or III. Results showed that a TLC threshold of 2250cells/mm^3 was the most accurate (0.73) predictor of CD4 cell counts ≤ 350 cells/ mm^3. This corresponded to a sensitivity of 88% for CD4 cell counts ≤ 200 cells/ mm^3 and would result in 21% of subjects being offered ART with CD4 cell counts > 350 cells/mm^3 (false positives). [26]

Results from a similar study examining the relationship between TLC and CD4 count among people living with HIV in Southern Ethiopia showed that a TLC of ≤1780cell/mm^3 had maximal sensitivity of 61% and specificity of 62% for predicting a CD4 cell count of < 200cell/mm^3. [30] This study concluded TLC had a low sensitivity and specificity when used as surrogate marker for CD4 count. [30] Anastos et al, found the strongest predictive value of TLC occurred at <850 cells/mm^3, but significant greater occurrence of ADI and death when HAART was initiated with TLC <1250 cells/mm^3 suggesting that an earlier threshold of TLC may be the better threshold for treatment because of the clinical benefit that can be obtained. [46]

A study done in Kampala Uganda titled, TLC of 1200 cells/mm^3 is not a sensitive predictor of CD4 lymphocyte count among patients with HIV disease, found a significant correlation between TLC and CD4 p≤0.0001. [6] However the WHO recommended TLC cut-off of 1200 cells/mm^3 to diagnose a CD4 Count <200 cells/mm^3, had low predictive value with a PPV of 100%, and NPV of 32%. The study therefore concluded that it requires a combination of TLC and clinical features in an algorithm to identify patients with CD4 cell counts less than 200 cells/mm^3 in Uganda. [6] Several studies have similar results, some of the TLC threshold found to be good predictors are TLC <1400 cells/mm^3 for CD4 count <200 cells/mm^3 and TLC <1700 cells/mm^3 (Kumarasamy et al) and TLC of 2250cell/mm3 for CD4 count of 350cell/mm^3 (Moore et al). The PPV of TLC as a predictor of CD4 count is low in studies done in Asia and elsewhere. Both PPV and NPV are affected by prevalence so in Sub-Saharan Africa where HIV prevalence among pregnant women is high may also present a high PPV. [24]

Utility of biomarkers HB and BMI as surrogates for CD4 count is suggested in several studies. Low HB (anaemia) and low BMI (weight loss) are independent risk factors for disease progression, CD4 counts of < 200 cells/mm^3 and early mortality. [2][24][26][35][46] It is the commonest haematological disorder in HIV with a prevalence of 30-40% in asymptomatic disease and up to 75-88 % in clinical AIDS. [2][49] Anaemia was

associated with an increased risk of all-cause mortality with a relative hazard (RH) of 2.06, for moderate anaemia and RH of 3.19 for severe anaemia, independent of CD4 cell count, WHO clinical stage, age, pregnancy, vitamin supplementation, and body mass index. [35] The accelerated decline in haemoglobin preceding the development of AIDS defines a point at which HAART could be initiated. This rapid decline generally precede AIDS by 1.2 years and occur when the CD4 Counts fall below 350 cells/mm^3.Therefore these markers may be suitable for staging HIV, monitoring disease and timing HAART initiation in resource-limited settings. [48]

Spacek et al in 2003 evaluated 3,269 individuals from the Johns Hopkins HIV Observational Cohort in a retrospective evaluation of the ability of TLC and haemoglobin to predict CD4 count. They concluded that TLC < 1200 cells/mm^3 was associated with CD4 count < 200 cells/mm^3 sensitivity for this threshold was low. Haemoglobin did seem to raise the predictability of low CD4 count by TLC in this study. Kumarasmy et al found that HB increased sensitivity at the expense of specificity. [47] They concluded the despite the failure to improve accuracy of TLC in predicting CD4 cell counts, using HB and BMI may still be of value in determining who should initiate ART in resource limited settings. [47] Recent studies have shown that low HB values and low BMI are independent risk factors for early mortality on ART in African settings and that in higher CD4 counts (200-350cell/mm^3) HB in an algorithm may actually improve predictability. [26]

Studies of nutritional status of HIV-infected patients have shown a substantial weight loss during the course of infection, and this phenomenon has often been considered as an unfavourable prognostic factor of survival. One such study confirmed the predictive role of weight loss in disease progression to AIDS independent of powerful indicators such as low CD4 cell count. Quetelet index has been used as an indicator of body adiposity and of adult chronic energy deficiency. This index requires only height and weight, thus allowing clinicians and researchers to determine status at a single point in time. [40] Therefore, as biological factors now take the forefront in patient management, it is important to be aware that such simple nutritional markers still should be mandatory in HIV patient management. [29]

The closest study done in this area in Kenya evaluated the usefulness of the CD4 cell count, CD4 cell percentage (CD4%), HIV type-1 load, TLC, BMI, and haemoglobin measured at 32 weeks' gestation as predictors of mortality in a cohort of HIV-1–infected women in Nairobi. The study concluded that TLC, BMI, and

haemoglobin had a limited predictive value for mortality. [21] This study evaluated these markers as surrogates or predictor of clinical outcome; in this case mortality as opposed to predictor of a surrogate marker.

Some methodological differences that could have weakened these studies are worth mentioning. Most of the studies were retrospective studies and some did not indicate whether tests were done from same blood samples. One of the limitations of the Moore et al study was that the analysis of the blood for CD4 and TLC was done five days later after blood was withdrawn. This could have affected the results. Besides if the physician is already aware of CD4 count levels before staging disease may result to biased judgement.

The WCS was found to be a poor predictor of patients with CD4 counts less than 200 cells/mm^3 in an African setting but the predictability but can be substantially improved by the use of simple laboratory tests and modified algorithms to maximize sensitivity at the cost of specificity. [24]

There is limited data for comparison in evaluating surrogate markers for CD4 count. This is because studies have looked at different populations in terms of race, geographical locations, sex and pregnancy. In addition these studies have also looked at different surrogate markers for CD4 count and often using these surrogate markers different combinations. The outcome variables (the marker or event being predicted) have also varied to include other surrogate markers, clinical events like ADI and mortality. There are even few studies as far as pregnancy is concerned.

As the scale-up of PMTCT programmes rises it is imperative that cheaper, reliable and scientifically proven tests to inform the decision to start HAART and perhaps for monitoring should be sought.

1.3 Justification

In poor resource settings like Kenya CD4 count is not always available thereby limiting access to ART by extension. Even where available the cost of doing a CD4 Count is prohibitive.

In light of expanding ART access through prevention of mother-to-child transmission (PMTCT) programs in resource-limited settings, cheaper and readily available

surrogate markers for CD4 Count are needed. Haemoglobin, HIV disease staging and BMI are routine measures and evaluations done in antenatal care clinics. Availability of these markers is guaranteed even in Health Institutions of low cadre where majority of pregnant women are attended. They do not incur extra cost and do not require expertise and sophisticated machines. Reaching more women with HAART is critical in preventing mother to child transmission which translates to reduced HIV national prevalence.

No studies have been done in Kenya comparing surrogate markers for CD4 Count and the effect of their combination on predictive accuracy among pregnant populations. Pregnancy is a period when TLC may vary and data from children and non-pregnant population may not necessarily be reflective of a pregnant population.

This study is in support of WHO's search for scientifically proven effective interventions and in the achievement of the millennium development goals. Discovery of cheaper effective diagnostics will translate to expansion of HIV care and treatment not only in Kenya but also the sub-Saharan region.

It was against this background that this study sought to evaluate the usefulness of TLC as surrogate marker for CD4 count among HIV infected pregnant mothers and determine the utility of a combination of HB, BMI and WCS in improving diagnostic accuracy.

1.4 Research Question

Does an algorithm of TLC in combination with WCS, HB level and BMI improve the predictive value of TLC as a surrogate marker for CD4 count to identify HIV infected pregnant with CD4 count < 350 cell/mm^3 and therefore those ante partum women eligible for HAART?

1.5 Statement of the Problem

The prevalence of HIV in sub Saharan Africa is high compared to the rest of the world and so is the prevalence of HIV among pregnant women. WHO has supported resource limited countries with treatment guidelines in order to scale-up ART with the aim of making ARVs universally accessible. Despite all these efforts still majority of

patients in immediate need of life-sustaining ART have not accessed it. These efforts are hampered cost of both ARVs and Diagnostics. The WHO recommended guidelines may not be optimal for African populations as pointed out in a number of studies.

CD4 count and Total Lymphocytes Cells are influenced by geographical, sex, age and race among other factors. WHO guidelines are based on clinical trials done in the western world and therefore may not represent the African population. TLC cut-off of 1200cell/mm^3 as predictor of CD4 count <200cell/mm3 has been disapproved. Delaying HAART until when CD4 count is that low has been associated with increased mortality even with treatment especially in the first year of therapy. WHO now recommends treatment at CD4 count < 350cells/mm^3.

TLC correlates with CD4 count but has low predictive value for low CD4 counts. Increasing the TLC cut-off and combining TLC with biomarkers that have been shown to independently predict HIV disease progression such as BMI and HB may improve the predictive value. The challenge will be to determine these cut-offs and use the algorithm in a way that the competing aims of sensitivity and specificity are reconciled.

1.6 Objectives of the study

Main Objectives

1. To determine the predictive accuracy of TLC in an algorithm with WCS staging, HB and BMI in predicting CD4 count below 350cells/mm^3 among HIV infected women.

2. Develop diagnostic model using the biomarkers TLC, HB, BMI, and WCS for eligibility of HAART in pregnant women.

Specific Objectives

- Determine the correlation between CD4 count and HB, BMI,WCS separately using Pearson's correlation.

- To assess the ability of a combination of TLC, WHO clinical staging, Haemoglobin and BMI to predict CD4 Count <350cells/mm^3 using linear regression.
- Determine the sensitivity, specificity, PPV and NPV for TLC, WCS, HB and BMI using 2 by 2 tables.
- Using the sensitivity and specificity values obtained in the objective above, optimal cut-offs for TLC, and their accuracy was determined.
- Develop clinical algorithm by combining these markers using different cut-offs and assess the predictive accuracy by calculating the area under ROC curves.

STUDY DESIGN AND METHODOLOGY

2.1 Study Design

This was a retrospective, cross-sectional study that evaluated utility of an algorithm of TLC in combination with biomarkers like HB, BMI, and WHO clinical staging in predicting CD4 count < 350 cells/mm^3.

2.2 Study Population and Period

The study population were pregnant, HIV positive women not already on HAART seen in the MTRH-AMPATH ANC clinic from 2005 to November 2010.

2.3 Inclusion criteria

1. ARV (HAART and PMTCT) naive patients
2. Pregnant women

2.4 Exclusion criteria

1. Incidental medical condition such as diabetes, heart or renal disease
2. Steroid use[33]

2.5 Sample size

Moore et al in a study conducted in Eastern Uganda which is a similar setting to, Kenya demonstrates that an algorithm that comprises TLC combined with HB and BMI for WHO stages I and II has an accuracy of 74% in predicting CD4 cell counts ≤ 350 cells/mm^3.[26] This corresponds to a sensitivity of 80% and specificity of 62%.

A minimum sample size of 362 patients was adequate to estimate the accuracy of the algorithm that comprises TLC combined with HB and BMI for WHO stages I,II and III in predicting ≤ 350 cells/mm^3 with 95% confidence (α=0.05) and an error margin of ±5%. The following formula [43] was used.

$$n = \frac{Z^2_{1-\alpha/2} P_1 (1-P_1)}{\delta^2}$$

=

Where;

n = sample size required

P= the specificity of the algorithm of TLC combined with HB and BMI for WHO stages I, II and III in predicting ≤ 350 cells/mm^3 is 62%. [26] This had a diagnostic accuracy of 74% and a sensitivity of 80%.Specificity of a test being the ability to indentify correctly those without disease is important in this study because it is grave to start HAART prematurely. Secondly unlike predictive accuracy, specificity is not affected by prevalence of the disease. Therefore specificity of 62% is used to calculate the sample size.

$Z_{1-\alpha/2}$ =Normal deviate corresponding to a 95% confidence interval in a two- tailed test (=1.96)

δ =error margin of 5%

$$n = \frac{(1.96)^2 * 0.62(1-0.62)}{(0.05)^2}$$

$$= 362.03238$$

$$= \mathbf{362\ patients}$$

2.6 Sample selection

Medical charts for pregnant mothers seen at MTRH-AMPATH centre clinic between Jan 2005 and November 2010 were randomly selected.

2.7 Study site

AMPATH formerly Academic Model for Prevention and Treatment of HIV/AIDS and now known as Academic model providing Access to Healthcare is a partnership between Moi University Faculty of Health Sciences and Moi Teaching Hospital in Eldoret, Kenya and Indiana University School of Medicine in the USA. AMPATH has 18 comprehensive HIV care clinics in urban and rural centres in western Kenya. Currently AMPATH has over 60,000 registered patients. The study evaluated only those HIV positive mothers who attended the MTRH-AMPATH PMTCT Clinic.

2.8 Clinical definitions

- Anaemia:

  CDC definition of anaemia in pregnancy is HB <11g/dl at 32 weeks. [21][34] Most women visit ANC in second trimester. For this research cut-offs of HB will be WHO cut-off points >10g/dl, ≤ 10/g/dl (for anaemia). [24]

- Body Mass Index is frequently used as a measure of over- or underweight both in clinical medicine and in research. [40] World Health Organisation (WHO) threshold values are as follows: [29][41]

  BMI <16.9 kg/m^2, *extreme underweight*

  BMI 17–18.4 kg/m^2 (underweight/ and

  BMI 18.5 kg/m^2 -24.9kg/m^2 (normal)

  BMI 25-29.9 kg/m^2 (Overweight)

  BMI >30 Obese

- TLC optimal cut-offs from reviewed studies has ranged from 850 to 2250cell/mm^3. [2][24] Categories used will be <1200, 1200-3000,>3000 cell/mm^3.

- Definition of WHO clinical stages I to IV (Refer to Appendix I for the definition of WHO clinical stage. Stages I, II, III will be considered. There is consensus that in Stage IV HAART should be initiated regardless of TLC or CD4 counts.

2.9 Data Collection Method

Data was extracted from patients' charts and entered into data proforma. (Appendix II).The selection of chart was done randomly. Those who did not meet inclusion criteria and/or had data missing from their charts were excluded. The principal investigator ensured that all patients whose selected met the Inclusion and Exclusion criteria.

2.10 Data Analysis

Data was entered into Microsoft excel sheet. It was cleaned and verified to ensure quality was maintained. Statistical Analysis was performed using SPSS version 15 and Stata 10.

BMI will be calculated using the Quetelet Index (weight in kg/height in m^2). Means and standard deviation of the continuous variables will be determined. Descriptive analysis of demographic, clinical and Laboratory study population characteristics.

The relationship between CD4 Count and TLC, HB, BMI and WCS on the other had will be determined using Pearson's correlation and logistic linear regression. Sensitivity, Specificity, PPV, NPV are calculated using 2 by 2 tables for all the predictor variables. ROC was generated using the sensitivity and specificity obtained to determine the predictive accuracy of each variable. Combination of TLC, HB, BMI and WCS will be done and Sensitivity, Specificity, PPV, NPV are calculated using 2 by 2 tables. ROC curves were used to demonstrate the effect of this combination on sensitivity and assess predictive accuracy. Data was presented in tables and graphs. Clinical algorithms were developed.

2.11 Study Strengths and Limitations

This was a retrospective study and the factors that affect precision such as circadian variation of CD4 count, presence of opportunistic and intercurrent infections could not be controlled.

Most pregnant mothers are given iron supplements in ANC and this may mask any drop of HB caused by HIV disease progression.

Inter-observer difference could not be controlled.

Period of study was long and machines used for CD4 count, TLC testing, weighing machines may have changed overtime as well as they were not standardized.

The main strength of this study was that data collection and recording at AMPATH is commendable and therefore of good quality. There was no data missing.

2.12 Ethical consideration

The study was conducted after approval by Ethics Review Committee of the University of Nairobi. A signed copy of the approval letter was presented to AMPATH Data manager and approval to collect data was given.
Confidentiality of data was be maintained. Patients' names were not be used in the data proforma. Data was be used for the sole purpose of research and learning.

RESULTS

A total of 362 subjects were included in this study. All were HIV positive, pregnant women and were not on any ARVs during the initial encounter the point at which data was collected. The mean (standard deviation) age was 26.97 (5.964) years ranging from 17-54years. Median age was 26 years. The majority were below 29 years (73.8%). Ages' between 15 and 24 years accounted for 32.9% of study population. Majority had primary level education and above 345(95.3%) and 256(70.7%) were married women.

Those with CD4 Count < 350cells/mm^3 were 161(44.5%) and ≥350cells/mm^3 were 201 (55.6%). The prevalence of anemia in this population using WHO cut-off point of hemoglobin level of below 10g/dl is about 30%. Haemoglobin and BMI mean (standard deviation) was 12(2.1) and 23.0(3.9) respectively. The majority 228(63%) had BMI within normal range. Only 14 women (3.9%) were extremely underweight and actually 20(5.5%) were obese.

The majority in this population were in WHO clinical stage I, 277(76.5%), Stage II, 35(9.7%),Stage III, 48(13.3%) and with only 2 women being classified as stage IV. A total of 261 mothers had TLC between 1200 and 3000cells/mm^3 and 37(10.2%) had TLC < 1200cells/mm^3.

Table 1: Socio-Demographic Characteristics of the Study Population

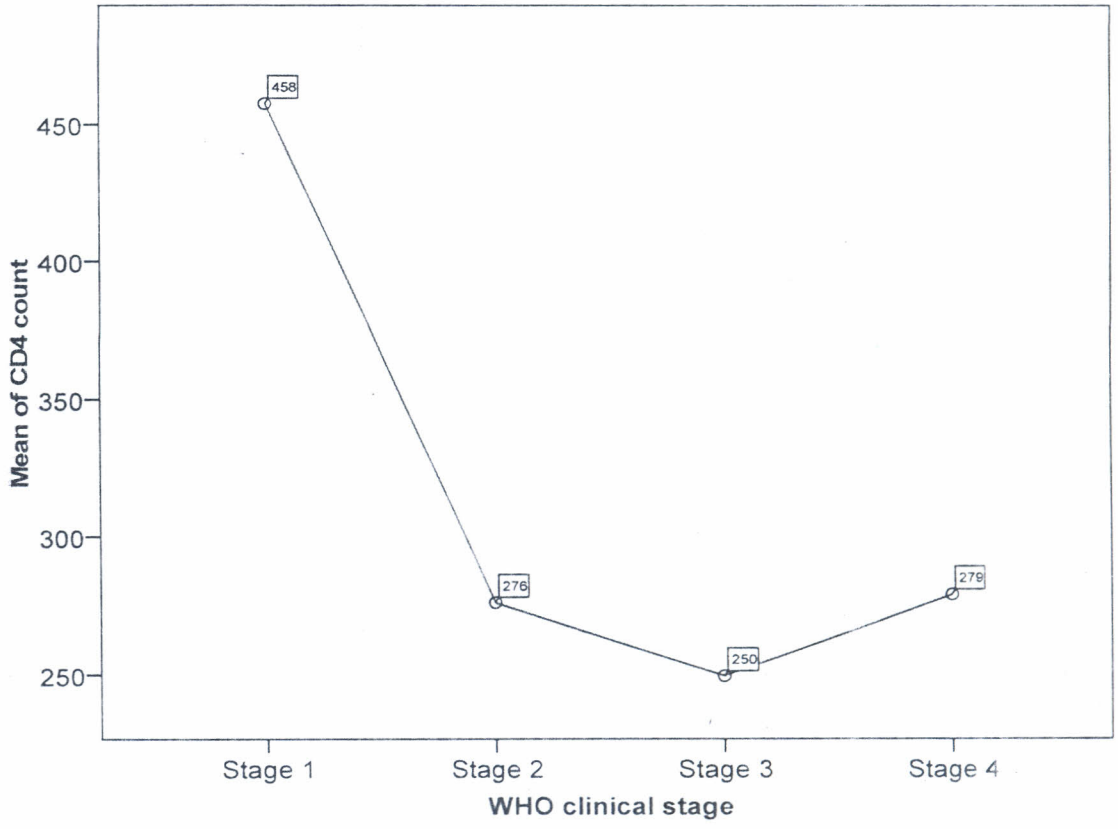
Characteristic	Frequency	%
Age group		
15-24	119	32.9
25-39	228	63.0
≥40 years	15	4.2
Marital Status		
Married	256	70.7
Single	53	14.6
Separated	32	8.8
Divorced	9	2.5
Windowed	12	3.3
Education Level		
None	17	4.7
Primary	235	64.9
Secondary	85	23.5
University/College	25	6.9
Parity		
Primigravida	67	18.5
Multigravida	246	68
Grandmultipara	49	13.5

Table 2: Clinical, Laboratory and Anthropometric Measures of the Study Population

Characteristic	Frequency	%
Gestational Age		
1-14 weeks	54	14.9
15-28 weeks	231	63.8
29-40 weeks	77	21.3
HB level		
>10g/dl	254	70.2
≤10g/dl	108	29.8
TLC (cells/mm^3)		
<1200	37	10.2
1200-3000	261	72.1
>3000	64	17.7
CD4 Count (cells/mm^3)		
<200	66	18.2
200-350	94	26.0
>350	202	55.8
WHO Clinical Stage		
I	277	76.5
II	35	9.7
III	48	13.3
IV	2	0.6
BMI		
<17 kg/m^2	14	3.09
17-18.4 kg/m^2	22	6.1
18.5-24.9 kg/m^2	228	63.0
25-29.9 kg/m^2	78	21.5
≥30 kg/m^2	20	5.5

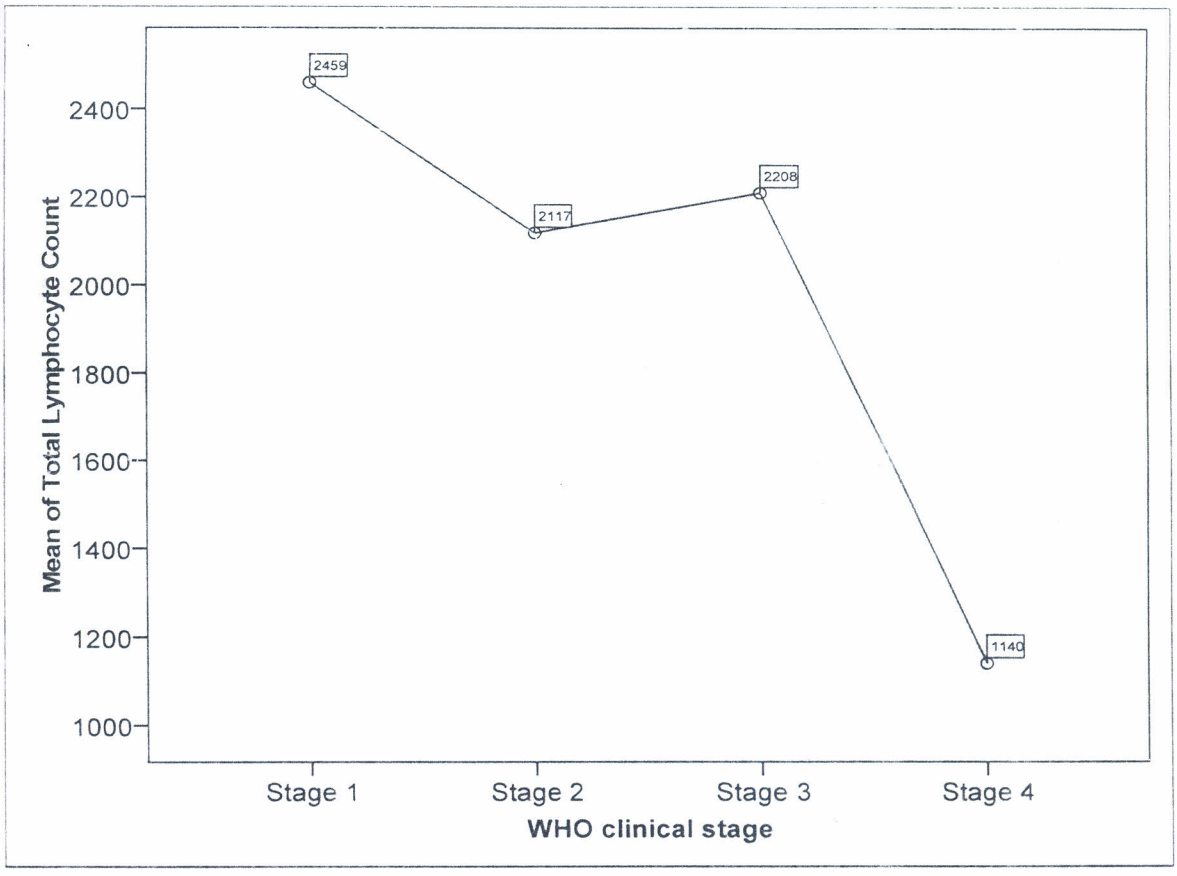
The mean standard deviation of CD4 count and TLC count were 405.37 (241) and 2228.41(1158) cells/mm^3 respectively. The mean CD4 counts across the 4 WHO Clinical Stages were significantly correlated at $p<0.001$.

Figure 1: Mean CD4 Count For WHO Clinical Stage



The mean CD4 counts showed a downward trend the higher the WHO Clinical stage was. The analysis of variance for CD4 count, F test is 13.35 ($p<0.001$) which indicates the means are significantly different.TLC F test is 1.141 with a p value of 0.33(not significantly different). This was unlike the means for TLC which did not show a linear decline trend from WCS I to IV. See Figure 2 below.

Figure 2: Mean TLC for WHO Clinical Stage



The correlation between CD4 and TLC was significant at $p<0.01$(Pearson's correlation= 0.192). R square (β coefficient) shown in the model in scatter plot above is small at 0.04. Using the equation above which represents the best fit linear regression line for all the scattered values CD4 count of <350 cells/mm3 is predicted by TLC of 850 cells/mm^3 p <0.05,(χ^2=4.66).The sensitivity and Specificity is 8% and 97%.

Figure 3: Correlation between CD4 Count and TLC (Cells/mm^3)

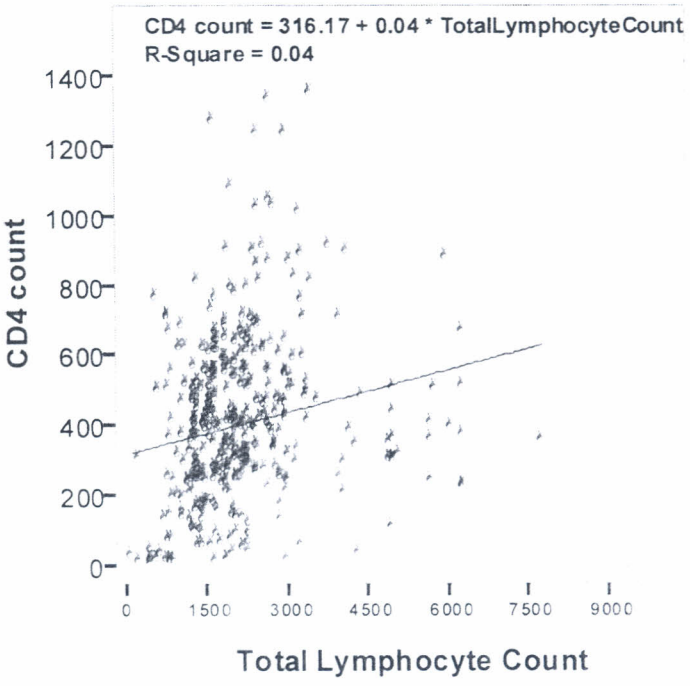
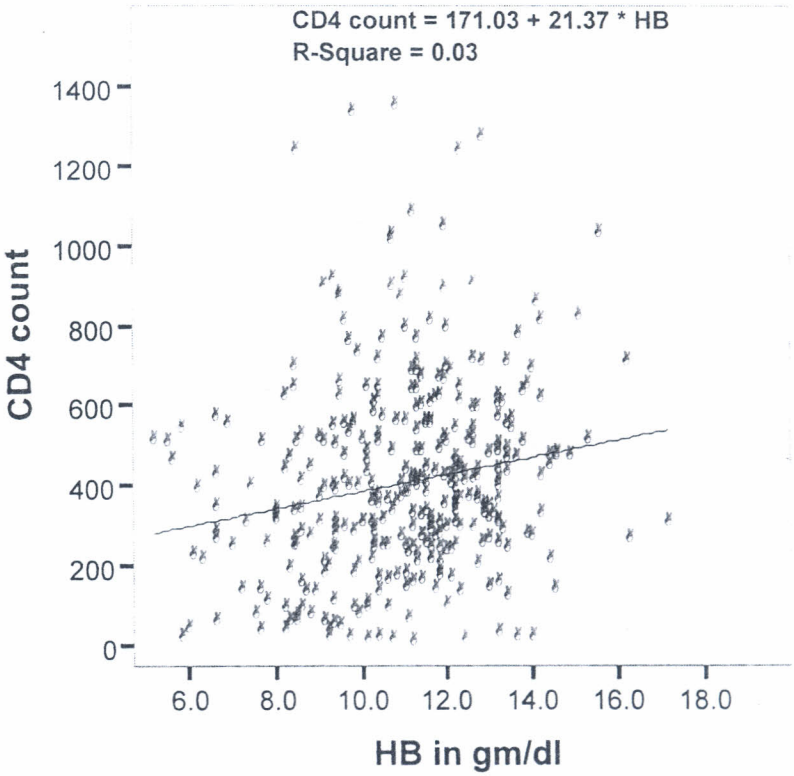
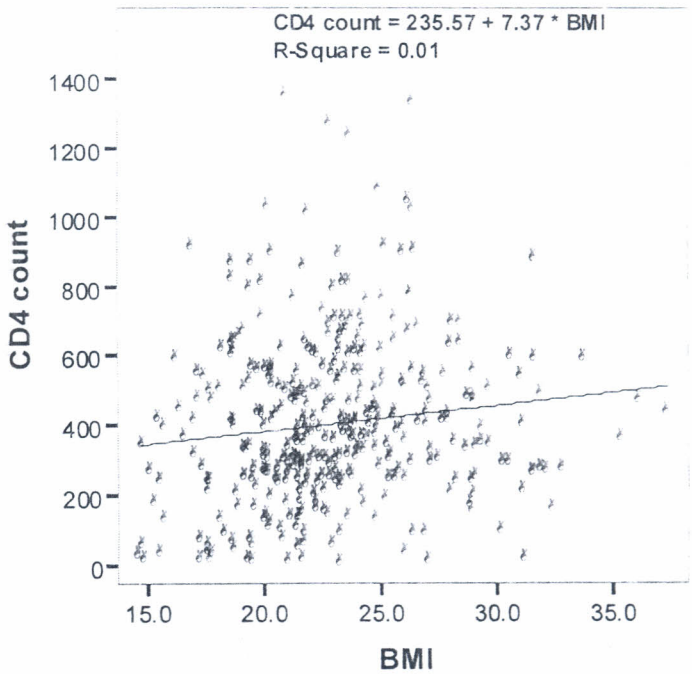


Figure 4: Correlation between CD4 Count (Cell/mm^3) and HB



The Pearson's correlation between CD4 count and HB was 0.184. This was closely related with that of TLC and was significant at $p<0.01$.The linear regression β coefficient was equally small at 0.03. Compared to TLC, HB has a lower predictive influence. The best fit regression line is given by the equation above. A CD4 Count of <350cells/mm^3 is predicted by HB of 8.4g/dl. The Sensitivity and Specificity of this threshold is 17.4% and 92.5% respectively.

Figure 5: Correlation between CD4 Count (cells/mm^3) and BMI



The Pearson's correlation between CD4 count and BMI was 0.120. This is low compared with both TLC and HB and was significant at $p<0.05$. Using the equation above BMI of 15.5kg/m^2 predicts CD4 Count of <350cells/mm^3. The Sensitivity and Specificity is 3.7% and 100% respectively.

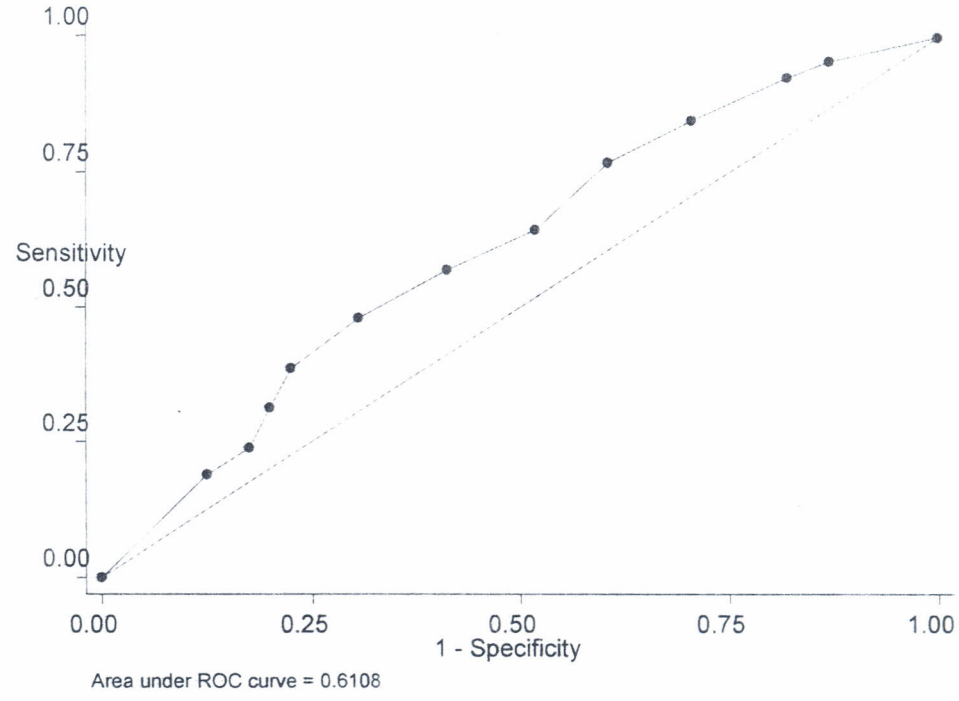
The sensitivity and specificity of different TLC cut-offs for predicting CD4 count < 350cells/mm^3 was determined as shown below. Cut-offs with high Sensitivity had low Specificity and vice versa. TLC of 1200 was found to be a poor predictor of CD4 count 350cells/mm^3 with a high specificity of 95% and a low sensitivity of 18%.

Table 3: Sensitivity & Specificity of TLC Cut-offs in Predicting CD4 Count <350cell/mm^3

TLC cut-off in cells/mm^3	sensitivity	specificity	NPV	PPV
<1000	12.52%	96.53%	74.10%	58.20%
≤1200	17.50%	94.55%	71.80%	59.10%
≤1400	28.75%	86.63%	63.00%	60.00%
≤1600	39.38%	76.73%	61.50%	59.00%
≤1800	48.13%	64.36%	60.50%	51.70%
≤2000	58.75%	56.93%	63.20%	52.50%
≤2200	69.38%	48.02%	64.20%	50.90%
≤2400	77.50%	38.61%	67.80%	50.20%
≤2600	80.00%	31.19%	65.98%	48.30%
≤2800	82.50%	23.76%	60.30%	45.80%
≤3000	87.50%	18.81%	64.60%	46.50%

The Receiver Operating Curve was generated using above sensitivity and specificity for the various TLC cut-offs. ROC is a graph of true positives (Sensitivity) against false positives (1 - Specificity).The area under the curve was 0.61 with a 95% confidence interval of 0.55-0.67.

Figure 6: ROC Curve for CD4 Count and TLC

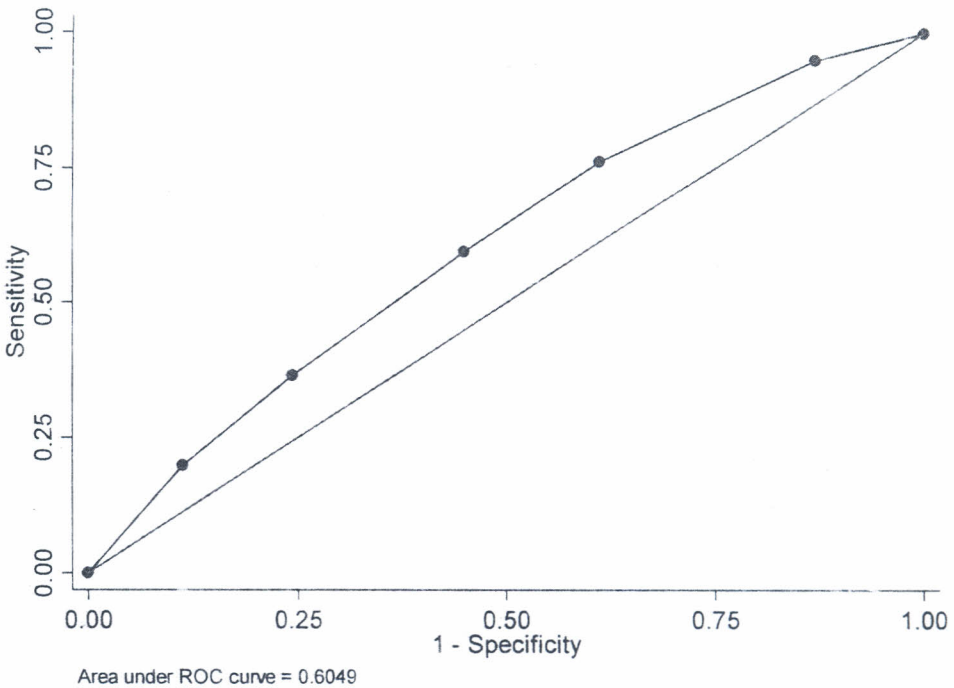


The Sensitivity and Specificity of various HB cut-offs were calculated as below. The best cut-off point is HB of <11g/dl with a Sensitivity and Specificity of 59.41% and of 55% respectively. The ROC for HB was calculated at 0.60 with a 95% confidence interval of 0.55 to 0.66.

Table 4: Sensitivity & Specificity of HB Cut-offs for CD4 Count < 350cells/mm^3

HB cut-off in g/dl	Sensitivity	Specificity	NPV	PPV
≤8	95.05%	13.13%	57.01%	62.96%
≤10	76.24%	38.75%	59.93%	66.10%
≤11	59.41%	55.00%	60.63%	56.48%
≤12	36.63%	75.63%	62.00%	52.47%
≤13	19.80%	88.75%	63.70%	48.56%
>13.1	37.80%	73.30%	63.90%	48.60%

Figure 7: ROC Curve for CD4 Count and HB



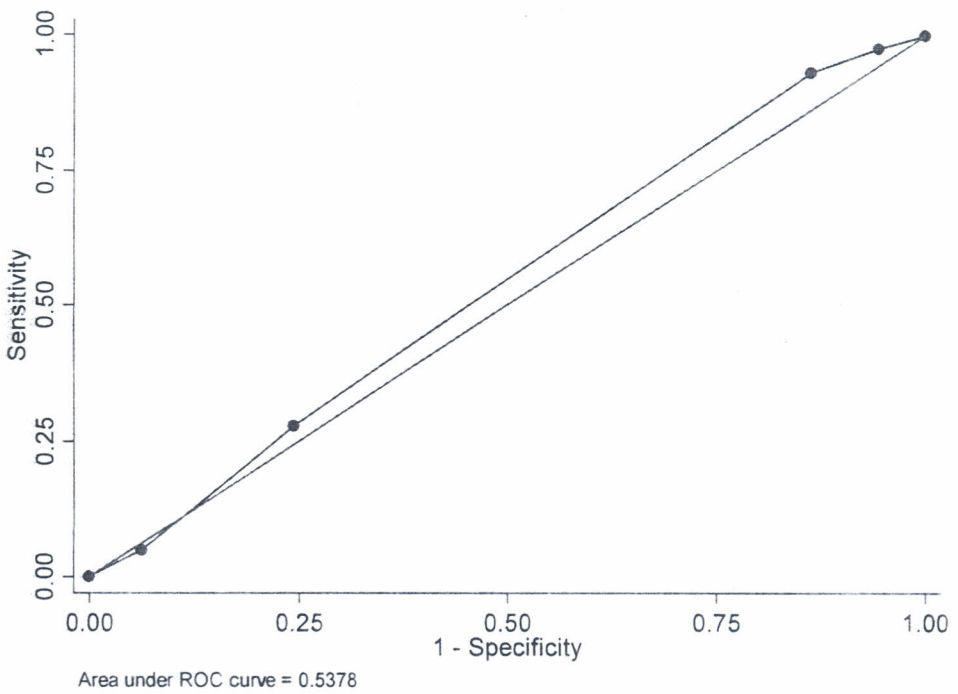
Sensitivity and specificity for various WHO BMI cut-offs were generated as shown below. Best cut-off was BMI of ≤24kg/m^2 with a Sensitivity and Specificity of 27.7% and 75.6% respectively.

Table 5: Sensitivity & Specificity of BMI Cut-offs for CD4 Count < 350cells/mm^3

BMI in cut-offs kg/m^2	Sensitivity	Specificity	+ve likelihood ratio	-ve likelihood ratio
≤16.9	97.52%	5.62%	1.0334	0.4400
≤18.4	93.07%	13.75%	1.0791	0.5041
≤24.9	27.72%	75.63%	1.1373	0.9557
≤29.9	4.95%	93.75%	0.7921	1.0139
≥30	0.00%	100.00%		1.0000

ROC curve was computed using the above Sensitivity and Specificity values. AUC was 0.54 with a 95% confidence interval of 0.49 to 0.59.See the ROC curve below

Figure 8: ROC Curve for CD4 Count and BMI



A TLC cut-off point of ≤1000 was chosen because it had a very high Specificity (97%) and PPV of (74%) for combination with other predictor variables to evaluate its effect on the low sensitivity (13%) of this threshold. Table 6 summarizes the Sensitivity, Specificity, Positive and Negative predictive values of each of the described algorithms. A three-stage algorithm was used to assess eligibility to HAART. It was comprised of a combination of TLC≤1000, WCS II&III and HB12g/dl. It assumed all subjects classified as WCS II &III are likely to be eligible if they had TLC≤1000 they were included in the treatment group. The remaining if they had HB<12 they were included from treatment group. It yielded a Sensitivity, Specificity, PPV, NPV, Youden's index (J) of 86.21%, 92.00%, 94.3%, 74.20%, 78.00% respectively. The area under curve was 89%. The algorithm of TLC≤1200 and HB <12 was second

best with Sensitivity, Specificity, PPV, NPV, and Youden's index (J) of 78.75%, 94.55%, 82.60%, 84.90% and 0.73 respectively. The area under the curve was 87%.

Table 6: Sensitivity, Specificity, PPV, NPV & Youden's Index of TLC, WCS, HB & BMI in different Combinations

TLC cut-off	Sensitivity	Specificity	PPV	NPV	J
Algorithm WCS II &III,TLC					
(≤1000)	18.97%	92.00%	85.7%	32.9%	0.11
(≤1200)	20.69%	92.00%	82.4%	33.3%	0.13
(≤1400)	24.14%	88.00%	77.8%	33.3%	0.12
(≤ 1600)	36.21%	76.00%	78.8%	33.9%	0.12
(≤1800)	44.83%	72.00%	80.0%	36.0%	0.17
(≤2000)	55.17%	68.00%	81.3%	39.5%	0.23
(≤2200)	67.24%	64.00%	69.9%	45.7%	0.31
Algorithm TLC,HB <12g/dl					
≤1000	77.50%	96.53%	92.00%	84.40%	0.74
Algorithm WCS II&III,TLC and HB <10g/dl					
(≤1000)	60.34%	92.00%	94.7%	50.0%	0.52
(≤1200)	**62.07%**	**92.00%**	**92.3%**	**51.1%**	**0.54**
(≤1400)	62.07%	88.00%	87.0%	50.0%	0.50
(≤ 1600)	68.97%	76.00%	86.3%	51.4%	0.45
(≤1800)	75.86%	72.00%	84.9%	56.3%	0.48
(≤2000)	77.59%	68.00%	84.2%	56.7%	0.46
(≤2200)	82.76%	64.00%	69.9%	61.5%	0.47

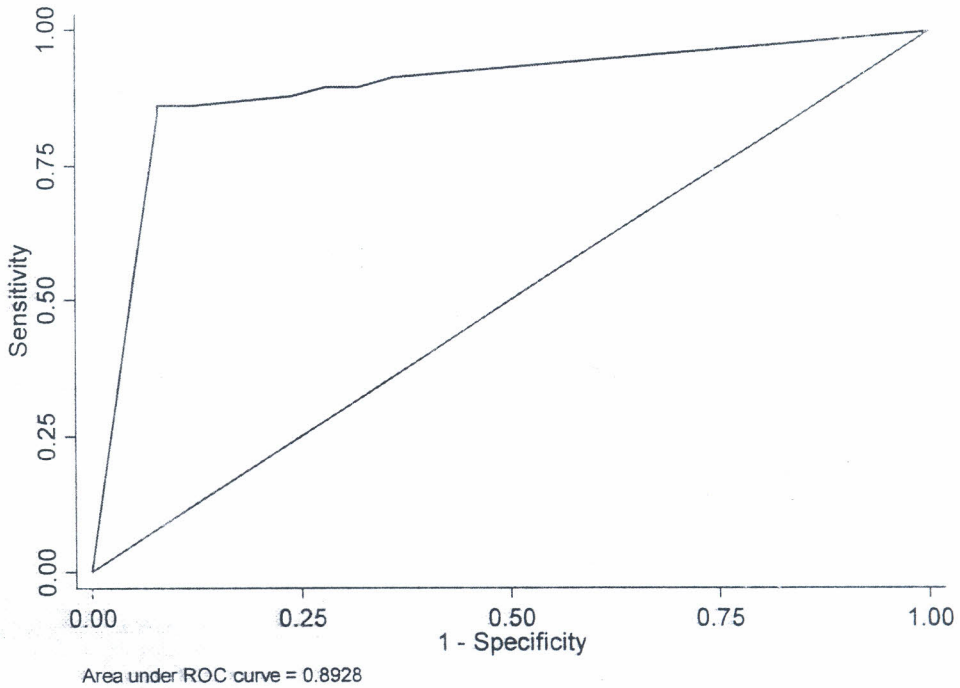
Algorithm of WCS II&III,TLC, and HB <12g/dl

(≤1000)	84.48%	92.00%	96.2%	71.9%	0.76
(≤1200)	**86.21%**	**92.00%**	**94.3%**	**74.2%**	**0.78**
(≤1400)	86.21%	88.00%	89.5%	73.3%	0.74
(≤ 1600)	87.93%	76.00%	88.1%	73.1%	0.64
(≤1800)	89.66%	72.00%	86.7%	75.0%	0.62
(≤2000)	89.66%	68.00%	85.5%	73.9%	0.58
(≤2200)	91.38%	64.00%	69.9%	76.2%	0.55

Algorithm of WCS II&III,TLC, HB <10g/dl and BMI <18.5

(≤1000)	65.52%	92.00%	95.1%	53.5%	0.58
(≤1200)	**67.24%**	**92.00%**	**92.9%**	**54.8%**	**0.59**
(≤1400)	67.24%	88.00%	87.8%	53.7%	0.55
(≤ 1600)	74.14%	76.00%	86.8%	55.9%	0.50
(≤1800)	74.14%	76.00%	86.8%	55.9%	0.50
(≤2000)	81.03%	68.00%	84.5%	60.7%	0.49
(≤2200)	84.48%	64.00%	69.9%	64.0%	0.48

Figure 9: ROC Curve for WCS II &III, TLC≤1000, HB<12



DISCUSSION

Majority of the women 231(63.8%) made their first antenatal visit during their second trimester consistent with what is reported in some studies. [30] A significant 77(21.3%) attended clinic for the first time in third trimester which can delay initiation of HAART whether for the purpose of PMTCT or lifelong therapy. However these women could have started antenatal clinic in other facilities and were only referred to our facility after they tested positive for HIV.

Those with CD4 Count < 350cells/mm^3 were 161(44.5%) and ≥350cells/mm^3 were 201 (55.6%). Nationally those eligible for HAART account for 32.1% and 67.9% with CD4 Count >350cells/mm^3 as reported by Kenya AIDS Indicator Survey, (KAIS) 2007. The prevalence of anemia in this population using WHO cut-off point of hemoglobin level of below 10g/dl is about 30%. WHO reports a prevalence of 30-40% in HIV positive populations and 8 of the women were on Iron supplements at this initial encounter.

This study has demonstrated that TLC correlates with CD4 cell count which confirms the finding of several other studies. [2][21][26][29][35][53] We saw the mean CD4 counts for each WCS were significantly correlated; the means dropped in a linear manner with each advanced clinical stage. For TLC, there was not a smooth linear decline between stages I and IV. There are studies that suggest that TLC does not follow a linear direction especially in early stage of HIV disease. It tends to correlate more with HIV disease progression only in late stages. [48]

Using linear regression the markers were found not to have perfect correlation as was indicated by a low β coefficient. However it is interesting to see that using Sensitivity and Specificity and algorithms in different combinations significantly improved the sensitivity. This study has shown that increasing TLC cut-off point increased Sensitivity at the expense of Specificity which corresponds with the findings of other studies. [6][24][39][47]

Another objective of this study was to evaluate optimal cut-off points that could be recommended at informing the decision to initiate HAART. The optimal threshold that was found for TLC in predicting CD4 Count <350cells/mm^3 using linear regression was TLC of 850cell/mm^3. This threshold however had a Sensitivity of only 8% with a false negative rate of 92%. A lot of patient eligible for treatment would not be

identified by this cut-off point. On the other hand only 3% of patients would be started on HAART prematurely.

The WHO recommended TLC cut-off of 1200 cells/mm^3 as a surrogate for CD4 count <350 cells/mm^3 had a low sensitivity of 17.5% and high specificity of 95%.Gupta et al found sensitivity and Specificity of 31% and 99% respectively. Our findings are consistent with several studies done in resource limited settings. [2][58] Specificity of 95% means that only 5% will be put on treatment prematurely. However the sensitivity is way too low at 18% meaning 82% eligible for HAART could not be identified by this cut-off point. This is not clinically acceptable.

The optimal cut-off point from this data when both sensitivity and specificity are given equal weight was TLC≤2200 with Sensitivity of 69% and Specificity of 48% and Youden's index of 0.19.This means a false positive rate of 32% and false negative rate of 49.5%. The high false positive and negative rates are clinically unacceptable. It is therefore difficult to recommend a single TLC threshold in determining eligibility to HAART (≤350cell/mm^3) especially when TLC is used alone.

The optimal cut-off point for HB was 8.4g/dl with a sensitivity of 17.4% and specificity of 92.5%. BMI optimal cut-off was 15.5kg/m^2 with a sensitivity of 3.7% and specificity of 100%. Extreme underweight given by BMI of <17kg/m^2 had a sensitivity and specificity of 5.6% and 97.5% respectively. All the three predictors variables (TLC, HB & BMI) for CD4 Count <350cells/mm^3 have very low sensitivity whereas the specificity is acceptably very high. TLC >850cell/mm^3, HB >8.4g/dl and BMI >15.5kg/m^2 are associated with CD4 Count >350cell/mm^3 but the reverse is not necessarily true.

The other important finding is that HB, BMI and WCS did significantly improve the sensitivity and predictive accuracy of TLC. HB of <8g/dl, <10g/dl and <12g/dl improved sensitivity up to 22.5%, 46.9%, 77.5% respectively. BMI and WCS >I improved sensitivity of TLC to 23.8% and 42% respectively.

The best algorithm was a three stage algorithm of a combination of WCS II&III, TLC ≤1000 and HB <12g/dl.

CONCLUSION

There is significant correlation between CD4 count and Total Lymphocyte count. These findings agree with other studies done locally and abroad.

This correlation is not perfect as indicated by a low β coefficient. The correlation between CD4 Count on one hand and HB and BMI on the other is not significant. This concurs with some studies (Brown et al). From the ROC curves the diagnostic value of these markers when used alone very low with values of 0.51-070 which indicates a fair test but is better than random guess.

No optimal cut-off point which is clinically acceptable could be found for recommendation in this study. Single TLC cut-off points should not be recommended when this marker is used alone to predict CD4 Count <350cells/mm^3. This agrees with WHO findings. [44]

HB, BMI, and WCS significantly improved the sensitivity of TLC in predicting CD4 Count <350cell/mm^3 and therefore eligibility to HAART. Clinical algorithms improved predictive accuracy for CD4 Count <350cells/mm^3.

STUDY LIMITATIONS

However the limitations of my study are worth mentioning. This was an analysis of retrospective data and there lacked control for confounding factors, effect of intercurrent infections, use of multivitamins, iron supplements and OI prophylaxis, standardisation of laboratory machine for (CD4 machines and Coulter counters for full blood count) and perhaps for weight loss MUAC be a more sensitive marker than BMI.

RECOMMENDATIONS

- TLC, HB, BMI, and WCS are useful surrogate markers for CD4 Count and can be used in resource poor settings to determine eligibility to HAART.
- Clinical algorithm can be used to predict eligibility for HAART in settings where CD4 Count testing is not available.

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APPENDIX I

ANNEX 1. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

Clinical stage I

1. Asymptomatic
2. Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Clinical stage II

3. Weight loss, <10% of body weight
4. Minor mucocutaneous manifestations (seborrhaic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Herpes zoster within the last five years
6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

And/or performance scale 2: symptomatic, normal activity

Clinical stage III

7. Weight loss, >10% of body weight
8. Unexplained chronic diarrhoea, >1 month
9. Unexplained prolonged fever (intermittent or consant), >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (i.e. pneumonia, pyomyoeitis)

And/or performance scale 3: bedridden <50% of the day during the last month

Clinical stage IV

14. HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention*
15. Pneumocystis carinii pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhoea >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes
20. Herpes simplex virus infection, mucocutaneous >1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
23. Candidiasis of the oesophagus, trachea, bronchi or lungs
24. Atypical mycobacteriosis, disseminated
25. Non-typhoid Salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy, as defined by the Centers for Disease Control and Prevention.†

And/or performance scale 4: bedridden >50% of the day during the last month

Note: both definitive and presumptive diagnoses are acceptable.

* HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month).

† HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

APPENDIX II

DATA PROFORMA

Subject code No.....

1. Age:

1. 15-19 years
2. 20-24 years
3. 25-29 years
4. 30-34 years
5. 35-39 years
6. 40-44years
7. > 45 years

2. Level of education

1. None
2. Primary
3. Secondary
4. University/college

3. Gestational Age:

1. 1 -14 weeks
2. 15 - 28 weeks
3. 29-40 weeks

4. Parity:

1. Para 0
2. Para 1-3
3. Para≥ 4

5. Marital Status

1. Married
2. Single
3. Separated
4. Divorced
5. Windowed

6. Haemoglobin level

1. > 12 g/dl
2. 8-12g/dl
3. < 8.0g/dl

7. WHO Clinical Stage

1 I
2 II
3 III
4 IV

8. CD4 Count:

1. >350
2. 200- 350cells/mm^3
3. < 200 cells/mm^3

9. Total Lymphocyte Count:

1. > 3000 cell/mm^3
2. 1200-3000 cell/mm^3
3. <1200 cell/mm^3

10. Body Mass index

Weight (kg)-

Height (cm)-

11. Current medication

1. Steroids
2. Others (specify)

APPENDIX III

USAID | AMPATH PARTNERSHIP	ADULT INITIAL ENCOUNTER FORM	Date: / /

me:	AMPATH ID:	Hospital #:	Child AMPATH ID:
tional ID Number:	HCT #:	pMTCT ID:	
e of Birth:	If Birthdate Unknown, Age at last Birthday: _____	Sex: □ M □ F	
e:	Location:	Sublocation:	

nic Location: MTRH Module: □1 □2 □3 □4 Chulaimbo □1 □2 Busia □1 □2

Amukura □ Burnt Forest □ Khunyangu □ Kitale □ Iten
Kabarnet □ Kapenguria □ Port Victoria □ Teso □ Mosoriot
Mt. Elgon □ Naitiri □ Turbo □ Webuye
UG District Hospital □ Satellite: _____ □ Other: _____

Category:
□ Pilot (PEPFAR)
□ NASCOP
□ Research
□ Other: _____

oint of HIV Testing: □ pMTCT □ VCT □ Mobile VCT □ HCT
□ TB Clinic □ Inpatient/DTC □ MCH □ Other: _____

ocial History:

How long did it take you to travel to clinic today?
- □ Less than 30 minutes
- □ Between 30 and 60 minutes
- □ Between 1 and 2 hours
- □ More than 2 hours

a. Have you ever attended school? □ Yes □ No

b. If yes, how many years of school have you completed? _____ Years

. Are you employed outside the home? □ Yes □ No

. Do you have electricity inside your home? □ Yes □ No

. Do you have water piped (from a tap) inside your home? □ Yes □ No

a. How many people usually live in your household or re staying with you now? _____

b. **Children** under 5 years of age? _____

a. Have you disclosed your HIV status to anyone? □ Yes □ No

7b. If yes, have you told any of the following people?
- □ Partner/spouse □ Other family member
- □ Friend □ Other household member
- □ Health care provider
- □ Other (specify): _____

10a. What is your current relationship status?
- □ Never married and not living with a partner
- □ Legally married: Number of wives _____
- □ Living with a partner
- □ Separated
- □ Divorced
- □ Widowed

10b. If widowed, suspicion of HIV as cause of death of spou
Yes □ No Year of death _____

10c. Discordant couple? □ Yes □ No □ Unknown

10d. Sexual Activity:
- □ Yes □ No - Spouse or partner suspected of sex partner outside of marriage/relationship
- □ Yes □ No - Patient has sex partners outside marriage or current relationship
- □ Yes □ No - Sexually active last 6 months
  Number of different partners _____

10e. How do you think you were exposed to HIV? (Check all that apply)
- □ Patient knows spouse or partner is HIV+
- □ Suspected exposure in prior relationship
- □ Blood Transfusion _____ (Year of Transfusion)
- □ History of Intravenous Drug Use
- □ Contaminated Needle Stick
- □ Unknown
- □ Other _____

Women Only:

8a. How many times have you been pregnant?_____

8b. How many children have you given birth to?_____

11a. Is the patient pregnant? □ Yes □ No
yes: _____ Weeks
If Yes: Enrolled in ANC? □ Yes □ No

11b. Is the patient Breast Feeding □ Yes □ No
(if yes, refer to nutrition for counseling and education)

APPENDIX III

. Number of your children living with you now: _____

. Number of your children living with you now <5 yrs old: _____

. Number of your children less < 18 months old _____

en Only:
How many children do you have? _____

12. Is the patient or their partner currently using any form of planning? □ Yes □ No
□ Condoms *(check all that apply)*
□ Oral Contraceptive Pill
□ Intrauterine Device
□ Sterilization / Hysterectomy
□ Natural Family Planning / Rhythm
□ Diaphragm / Cervical Cap
□ Injectable Hormones (Depo-Provera or Norplant)
□ Other:

a. Do you smoke cigarettes? □ Yes □ No
Stopped How long ago? ___wks ___mos ___yrs

13b. If Current or Past Cigarette Use:
Sticks per day: _____ # Years of Use: _____

c. Do you sometimes drink alcohol? □ Yes □ No
Stopped How long ago? ___wks ___mos ___yrs

13d. If you drink alcohol or used to drink alcohol, what kind d you usually drink? *(tick all that apply)*
□ Beer □Spirits/Liquor □Wine
□ Chang'aa □ Busaa

e. How often did you have a rink containing alcohol in the last ear?
□ Never
□ Monthly or less
□ 2 to 4 times a month
□ 2 to 3 times a week
□ 4 to 5 times a week
□ 6 or more times a week

13f. How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?
□ 0 drinks
□ 1 to 2 drinks
□ 3 to 4 drinks
□ 5 to 6 drinks
□ 7 to 9 drinks
□ 10 or more drinks

13g. How often did you have six or drinks on one occasion in the past y
□ Never
□ Less than monthly
□ Monthly
□ Weekly
□ Daily or almost daily

eview of Systems:

. CHIEF COMPLAINT: □ Feeling well □ Having symptoms

. General : □ No complaints
□ Fever □ Chills □ Weight loss □ Night Sweats □ Rash □ Fatigue □ Weight gain
omments:

. HEENT : □ No complaints □ Hearing difficulties □ Vision difficulties □ Swallowing difficulties
omments:

. Cardiopulmonary : □ No complaints
□ Cough O days O weeks O months
□ Cough productive O white O purulent O blood
□ SOB O days O weeks O months
□ At rest □ On exertion
□ Pneumonia in the past 2 years
□ Chest pain O days O weeks O months
Location: □ substernal
□ right □ left □ anterior □ posterior
Quality: □ Pleuritic □ Sharp
□ Pressure □ Burning

TB: □ Currently on treatment □ Defaulted _____(year)
□ Treatment completed _____ (year)
□ Known exposure to household contact with TB
omments:

. Gastrointestinal : □ No complaints
□ Abdominal pain □ Poor appetite □ Nausea O days O weeks O months O Continuous
□ Hx of jaundice □ Vomiting O days O weeks O months O Continuous
□ Diarrhea O days O weeks O months O Continuous
omments:

. Genitourinary: □ No complaints
□ LMP _____ Menstrual Cycle: □ Regular □ Irregular □ Amenorrhea □ Post-Menopausal
□ Vaginal discharge O days O weeks O months □ UTI
□ Urethral discharge O days O weeks O months □ Hematuria □ Circumcised?: □ Yes □ No
omments: _____

APPENDIX III

). **Musculoskeletal:** G No complaints
□ Joint pains □ Swelling of joints □ Edema of legs □ Muscle pain □ Pain in the legs / feet
omments:

. **Central Nervous System :** □ No complaints
□ Paresthesia □ Focal Weakness □ Seizures □ Headache
□ Depression □ Confusion □ Mental Illness □ Memory problems
omments:

ospitalizations

2a. Has the patient been hospitalized in the previous year? □ Yes □ No

2b. If yes, how many hospitalizations did the patient have in the past year? _____
Briefly describe the reason(s) for hospitalizations:

ledication History

3. **Allergies:**
enicillin Allergy □ Yes □ No Specify Reaction _____
ulfa Allergy □ Yes □ No Specify Reaction _____
ther Allergy □ Yes □ No Name of drug/product _____ Specify Reaction _____

4a. Is the patient currently taking any of the following antiretroviral medications? □ Yes □ No
Reason for Use □ pMTCT □ PEP □ Treatment Date Started: ___/_____ Date Stopped ___/_____
(Tick all that apply) m m
n m y y y y
Combination: □ Combivir □ Triomune-30 □ Triomune-40 □ Truvada
ndividual:□ Nevirapine(NVP) □ Lamivudine(3TC) □ Zidovudine(AZT) □ Stavudine-30(D4T-30)
Stavudine-40(D4T-40) □ Efavirenz(EFV) □ Abacavir(ABC) □ Aluvia/(Kaletra) □ Didanosine-125(DDI)
Didanosine-200(DDI) □ Tenofovir(TDF) □ Indinavir(IDV) □ Other::

24b. Has the patient used any antiretroviral medications in the past (other than those ticked in 24a)? □Yes □ No
Reason for Use □ pMTCT □ PEP □ Treatment Date Started: ___/_____ Date Stopped ___/_____
(Tick all that apply) m m
m m y y y y
Combination: □ Combivir □ Triomune-30 □ Triomune-40 □ Truvada
Individual:□ Nevirapine(NVP) □ Lamivudine(3TC) □ Zidovudine(AZT) □ Stavudine-30(D4T-30)
40(D4T-40) □ Efavirenz(EFV) □ Abacavir(ABC) □ Aluvia/(Kaletra) □ Didanosine-125(DDI) □ Did
□ Tenofovir(TDF) □ Indinavir(IDV) □ Other::

25. **Other Current Medications:**

PCP Prophylaxis: □ None □ Septrin □ Dapsone

TB Prophylaxis: □ None □ INH

TB Treatment: □ None □ Rifater (RHZ) □ Rifafour(RHZE) □ Ethizide (EH) □ Rifinah (RH) □ Rifampici
Date_____ □ INH □ Pyrazinamide □ Ethambutol □ Streptomycin □Other:

Cryptococcus Tx: □ None □ Diflucan

Other Drugs:

PHYSICAL EXAMINATION

26. **Vitals:**
BP _____/_____ Pulse_____rate/min Resp Rate_____ Temp[Co]_____ SaO2 _____%

Wt kg Height cm Karnofsky Score _____%

Karnofsky Score:
100% = Normal health
90% = Minor Symptoms
80% = Normal Activity with some effort
70% = Unable to carry on normal activity, able to care for oneself
60% = Requires help with personal needs
50% = Disabled
40% = Requires considerable assistance, medical care
30% = Severely disabled, in hospital
20% = Very sick, active support needed
10% = Moribund (near death)

27. **General Exam:** □ Temporal wasting Comments:

28. **Skin** □ Normal □ Abnormal □ Rash □ Kaposi sarcoma

APPENDIX III

mments:

Lymph Nodes □ Normal □ Abnormal Comments:
ubmandibular □ cervical □ inguinal □ supraclavicular □ axillary

HEENT □ Normal □ Abnormal
Eyes: □ Sclera icteric □ Conjunctiva pale □ Fundal abnormality
Ears: □ Cerumen impaction □ TM injected
Neck: □ Trachea deviated □ Nuchal rigidity
Oropharynx: □ Thrush □ Kaposi sarcoma □ Significant dental caries

Chest □ Normal □ Abnormal
rcussion: □ Dullness
scultation: □ Breath sounds diminished □ Bronchial breath sounds □ Rhonchi /Wheezes □ Crepitations
mments:

Heart □ Normal □ Abnormal
Evidence for enlargement: □ LV lift □ RV lift
Abnormal Sounds: □ S3 Gallop □ Pericardial friction rub
Murmurs: □ Systolic Ejection Murmur □ Holosystolic Murmur □ Diastolic Decrescendo □ Diastolic Rumble
mments:

Abdomen □ Normal □ Abnormal
□ Tender to palpation Location_____ □ Ascites □ Mass
□ Hepatomegaly ____ (cm below costal margin) □ Splenomegaly _____ (cm below costal margin)
mments:

Urogenital □ Normal □ Abnormal □ Not done Comments:

Extremities □ Normal □ Abnormal □ Edema □ Leg ulcers □ Cellulitis □ Kaposi sarcoma
mments:

Musculoskeletal □ Normal □ Abnormal
Comments:

Neurologic □ Normal □ Abnormal
Cranial nerve abnormality □ Decreased sensation lower extremities □ Abnormal gait □ Focal weakness
Comments:

Psychiatric □ Normal □ Abnormal □ Depressed □ Dementia / confused
Comments:

Does the patient currently have, or has the patient ever had, any of the following conditions?
ill in the appropriate box next to each indicator condition *P=Presu*
C=Confirmed

WHO Stage 1		**WHO Stage 4**	P	C
symptomatic HIV Infection	□	HIV Wasting Syndrome	□	□
ersistent Generalized Lymphadenopathy (PGL)	□	Pneumocystic Pneumonia	□	□
WHO Stage 2		Recurrent severe bacterial pneumonia	□	□
Weight Loss ≤ 10% of Body Weight	□	Chronic Herpes Simplex (mucocutaneous>1 mo, or any visceral)	□	□
ecurrent Upper Respiratory Tract Infections bacterial)	□	Candidiasis (Oesophageal, Bronchi, Trachea, or Lungs)	□	□
erpes Zoster	□	Extrapulmonary Tuberculosis	□	□
ngular Cheilitis	□	Kaposi's Sarcoma (KS)	□	□
ecurrent Oral Ulceration	□	Cytomegalovirus Disease (retinitis or other organs)	□	□
apular pruritic eruptions	□	Toxoplasmosis, CNS	□	□
eborrheic Dermatitis	□	HIV Encephalopathy	□	□
ungal Nail Infections	□	Cryptococcosis,Extrapulmonary (includes meningitis)	□	□
WHO Stage 3	**P** **C**	Disseminated non-TB mycobacterial infection	□	□
Weight Loss > 10% of Body Weight	□ □	Progressive Multifocal Leukoencephalopathy PML)	□	□
Unexplained Chronic Diarrhea (>1 month)	□ □	Chronic Cryptosporidiosis (> 1 month duration)	□	□
ersistent Oral Candidiasis (Thrush)	□ □	Chronic Isosporiasis	□	□
Unexplained Prolonged Fever (intermittent or onstant, >1 month above 37.5° C)	□ □	Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)	□	□
ral Hairy Leukoplakia	□ □	Recurrent septicemia (including non-typhoidal Salmonella)	□	□
ulmonary Tuberculosis	□ □	Lymphoma (cerebral or B-cell non-Hodgkin)	□	□

APPENDIX III

ere Bacterial Infections (ie pneumonia, pyema, pyomyositis, bone/jt infection, ningitis, bacteremia)	□	□	Invasive cervical carcinoma	□	□
ute necrotizing stomatitis, gingivitis, or riodontitis	□	□	Atypical disseminated leishmaniasis	□	□
explained anaemia (<8 g/dl), neutropaenia .5 x 109/L), and/or chronic mbocytopaenia (<50 x 109/L)	□	□	Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy	□	□

Tests

st	Result	Test Date	Test	Result	Test Date
WBC / mm3			9. CD4		
Hgb g / dL			10. CD8		
MCV			11. CD4 %		
Platelets / µ L			12. VDRL		
ALC / mm3			13. HIV Test (Rapid)		
SGPT			14. HIV Test (Long ELISA)		
Creatinine mmol / L			15. Viral Load		
Other:			16. other		
CXR Code:			Codes : 0=normal 1=Pl Effusion 2=Infiltrate 3=milliary 5=cav 4=Diffuse abn/non-milliary 6 - Cardiomegaly 7=other abnormali		

HIV-related Diagnoses/Problems

oblem	Remove	Resolved	Problem	Remove	Resolved
	□	□	5.	□	□
	□	□	6.	□	□

n HIV-related Diagnoses/Problems ** For Other Problems, tick box only if problem needs to be added to or r*
from summary sheet

oblem	Add	Remove	Problem	Add	Remove
	□	□	4.	□	□
	□	□	5.	□	□

. Plan:

RVs: □ None □Start ARVs □Continue Regimen □Restart □Change Dose □Drug Substitution
□Change Regimen □ Stop All
Reason to start ARVs: □ Treatment □ Total pMTCT
Reason for stop/change: □ Failure □ Completed T-pMTCT □ Toxicity_____ □ Other____

Eligible for ARVs but not started:
□ Due to cap □ OI/TB tx □ Patient Refused □ Adherence Concerns □Other_____
*If **start or change**, tick new regimen:*
mbination: □ Combivir □ Triomune-30 □ Triomune-40 □ Truvada
Individual:□ Nevirapine(NVP) □ Lamivudine(3TC) □ Zidovudine(AZT) □ Stavudine-30(D4T-30)
40(D4T-40) □ Efavirenz(EFV) □ Abacavir(ABC) □ Aluvia/(Kaletra) □ Didanosine-125(DDI)
200(DDI) □ Tenofovir(TDF) □ Indinavir(IDV) □ Other:: _____

APPENDIX III

CP Prophylaxis: □ None □ Start □ Continue Regimen □ Change Regimen □ Stop

eason for stop/change: □ CD4>200 □ Toxicity_____ □ Other_____
ew Drugs: □ Septrin ____tabs/day □ Dapsone_____ mg/day

B Prophylaxis: □ None □ Start INH □ Continue INH □ Stop INH

eason for stop/change: □ Completed □ Active TB □Toxicity_____ □ Other_____

B Treatment: □ None □ Start Induction □ Change to Continuation □ Continue Regimen
Restart/Retreatment Regimen □ Defaulter Regimen (using Streptomycin) □ MDR Regimen □ Stop All
eason for stop/change: □ Completed □ Toxicity_____ □ Other_____
ew Drugs:
Rifater (RHZ) _____tabs/day □ Rifafour (RZHE) _____tabs/day □ Ethizide (EH) _____tabs/day
Rifinah (RH)_____tabs/day □ Rifampicin_____mg/day □ INH_____mg/day
Pyrazinamide_____mg/day □ Ethambutol_____mg/day □Streptomycin_____mg/day
Other:

3. Additional Drugs (ordered at the time of the initial visit)

)rug	**Strength**	**Sig**	**Drug**	**Strength**	**Sig**
.			4.		
2.			5.		
3.			6.		

Patient Plan Comments:

44. What tests will be ordered for the patient? □ None
□ Complete Blood Count □ ALT □ AST □ CXR □ Radiology Test (specify):
□ CD4 Count Assay □ Creatinine □ HIV ELISA □ Sputum for AFB
□ VDRL □ Electrolytes □ HIV Viral load □ Pregnancy Test
□ Other (specify):

45. What referrals will be made for the patient? □ None
□ Social Support Services □ Psychosocial counseling □ Disclosure counseling
□ Family Planning services □ Reproductive Health □ TB treatment/DOT program
□ Nutritional support □ Adherence Counseling □ Alcohol counseling/ support groups
□ Mental Health Services □ Other referral (specify):
□ Inpatient care/Hospitalization: (□ MTRH □ Local Health Centre/Hospital □ Other Facility:_____)

46. When is the patient's next appointment? *Fill in appropriate box:*
□ 1 week □ 2 weeks □ 1 month □ 3 months □ 6 months □ Other (specify):

47. Next Scheduled Appointment Date __ __ / __ __ / __ __ __ __
d d m m y y y y

Form completed today by: Clinical Officer_____Provider #:_____

Nurse _____ Provider #:_____

Physician _____ Provider #:_____

KENYATTA NATIONAL HOSPITAL
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Ref: KNH-ERC/ A/415

4th March 2010

Dr. Winfred Mwangi
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr. Mwangi

RESEARCH PROPOSAL: "UTILITY OF AN ALGORITHM OF TOTAL LYMPHOCYTE COUNT, HEMOGLOBIN LEVEL, BODY MASS INDEX AND WHO CLINICAL STAGING AS SURROGATE MARKERS FOR CD4 COUNT TO DETERMINE THE ELIGIBILITY FOR HAART AMONG HIV INFECTED ANTEPARTUM WOMEN IN AMPHATH" (P2/01/2010)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above cited research proposal for the period 4th March 2010 – 3rd March 2011. However, address the following issues:

- Use KNH/UON-ERC format.
- Address the minor correction.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

DR. L. W. MUCHIRI
AG. SECRETARY, KNH/UON-ERC

c.c. Prof. K. M. Bhatt, Chairperson, KNH/UON-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The HOD, Records, KNH
The Chairman, Dept. of Clinical Medicine & Therapeutics, UON
Supervisors: Dr. James M. M'Imunya, Dept.of Obs/Gynae. UON
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