

CORRELATION OF WHO CLINICAL STAGING WITH CD4 COUNTS IN ADULT HIV/AIDS PATIENTS AT KNH

A DISSERTATION SUBMITTED IN PART FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE)

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DECLARATION

I certify that this dissertation is my original work and has not been presented for a degree in any other university.

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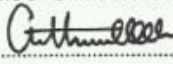
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DEDICATION

This study is dedicated to my dad; to whom I owe everything.

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First and foremost, I would like to thank our Almighty Father; Through Him all things are made possible.

My eternal gratitude to my family and friends, for their unwavering support. To my editor-in-chief (Tina); I shall forever be indebted to you.

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TABLE OF CONTENTS

	PAGE
A - Abstract.....	1
1.0 Abbreviations	2
2.0 Introduction: HIV in Kenya	4
3.0 History of HIV infection.....	4
4.0 Literature review	
4.1 Mechanism of HIV disease.....	5
4.2 Anatomical home of HIV disease.....	7
4.3.1 Role of CD4 in manifestation of HIV disease.....	8
4.3.2 WHO clinical Staging.....	10
4.4 Role of surrogate markers in assessing disease progression.....	11
4.5 Use of WHO clinical staging as a surrogate for CD4 count.....	12
5.0 Study justification.....	18
5.1 Research Question.....	18
6.0 Study objectives.....	18
7.0 Methodology.....	19
7.1.1 Sample size calculation.....	20
7.1.2 Sampling method.....	20
7.2 Recruitment of patients.....	21

	PAGE
7.3 Clinical Methods	22
7.4 Laboratory and radiological methods.....	22
7.5 Data analysis	23
8.0 Ethical considerations.....	24
9.0 Results.....	25
10.0 Discussion.....	31
11.0 Limitations.....	36
12.0 Recommendations	36
13.0 References.....	38
14.0 Appendices	
Appendix 1- Consent Explanation.....	44
Appendix 2- Consent Form.....	46
Appendix 3- Screening Profoma	47
Appendix 4- Partec Cytoflow Method.....	51
Appendix 5- 2005 Revised WHO Clinical Staging.....	52
Appendix 6- WHO clinical Staging-Presumptive and definitive criteria for recognizing HIV/AIDS related events	55
Appendix 7- CDC classification.....	65
Appendix 8- Original WHO 1990 clinical staging.....	67

LIST OF FIGURES

	PAGE
Figure 1: HIV prevalence KAIS 2007.....	3
Figure 2: Natural history of HIV RNA levels and CD4 count.....	9
Figure 3: Manifestation of opportunistic infections with fall in CD4 counts..	17
Figure 4: Recruitment flow chart for the patients.....	25
Figure 5: WHO clinical staging and CD4 counts in the study patients.....	27

LIST OF TABLES

	PAGE
Table 1: CD4 levels in relation to the severity of immunosuppression.....	13
Table 2: Kaagayi et al- Ability of WHO clinical staging to predict CD4 T cell count of 200 cell/ μ l.....	13
Table 3: Jaffar et al-Ability of WHO clinical staging to predict CD4 T cell count of 200 cell/ μ l.....	14
Table 4: Edathoju et al-WHO clinical staging and mean CD4 T cell count.....	15
Table 5: Kassa et al- WHO clinical staging and median CD4 T cell count.....	16
Table 6: Socio-demographic profile of study patients.....	26
Table 7: Correlation of WHO clinical staging and CD4 counts in the patients.	26
Table 8: Ability of WHO clinical staging to predict CD4 of 200.....	28
Table 9: Ability of WHO clinical staging to predict CD4 of 350.....	28
Table 10: Prevalence of HIV clinical events in the patients.....	29
Table 11: Chest Radiograph findings.....	30

ABSTRACT

OBJECTIVE: To determine the degree of correlation between the WHO clinical staging and CD4 T cell counts in HIV/AIDS adults at Kenyatta National Hospital, Nairobi.

DESIGN: Cross-sectional study.

SETTING: Kenyatta National Hospital, Nairobi.

SUBJECTS: 152 newly diagnosed HIV patients were recruited prospectively. Patients were first staged using the 2005 WHO clinical staging and then blood drawn for CD4 count.

RESULTS: The mean age in the study was 35 years, with females comprising 56.2% of the study group. The mean CD4 counts were 455, 420, 203 and 92 for WHO Stage 1, 2, 3 and 4 respectively. The sensitivity of the WHO clinical staging to predict CD4 counts of >350 cells/ μ l was 63% with a specificity of 82%. The commonest HIV clinical events were bacterial infections(33%), severe weight loss(28%) and tuberculosis(27%).

CONCLUSIONS: There was correlation between the WHO clinical staging and expected CD4 T cell count. However, the sensitivity was low and missed over a third of the patients in need of HAART. Majority of the patients presented in severe disease in need of HAART at the onset of their HIV diagnosis with 107 (70.3%) of the patients with Stage 3 or 4 disease and 114 (75%) of patients with CD4 counts of <350 cells/ μ l.

KEY WORDS: HIV, AIDS, CD4 counts, Kenyatta National Hospital, Nairobi

1.ABBREVIATIONS

AAFBs- Acid Alcohol Fast Bacilli

AIDS- Acquired Immune Deficiency Syndrome

BMI- Body Mass Index

CCC- Comprehensive Care Clinic

CCR5- Chemokine receptor type 5

CD4 - Cluster of Differentiation 4

CD8- Cluster of Differentiation 8

CDC- Centre for Disease Control

CTL- Cytotoxic T lymphocytes

CXCR4- Chemokine receptor type 4

DC-SIGN-dendritic-cell-specific intercellular adhesion molecule 3-grabbing nonintegrin

HAART- Highly Active Antiretroviral Therapy

HIV- Human Immunodeficiency Virus

KDHS- Kenya Demographic Health Survey

KAIS- Kenya AIDS Indicator Survey

KNH- Kenyatta National Hospital

NASCOP- National AIDS and STI Control Program

OI- Opportunistic infection

PITC- Provider Initiated Testing and Counseling

SIV- Simian Immunodeficiency Virus

TB- Tuberculosis

TBC- Total Blood Count

U/E/C- Urea/ Electrolytes/ Creatinine

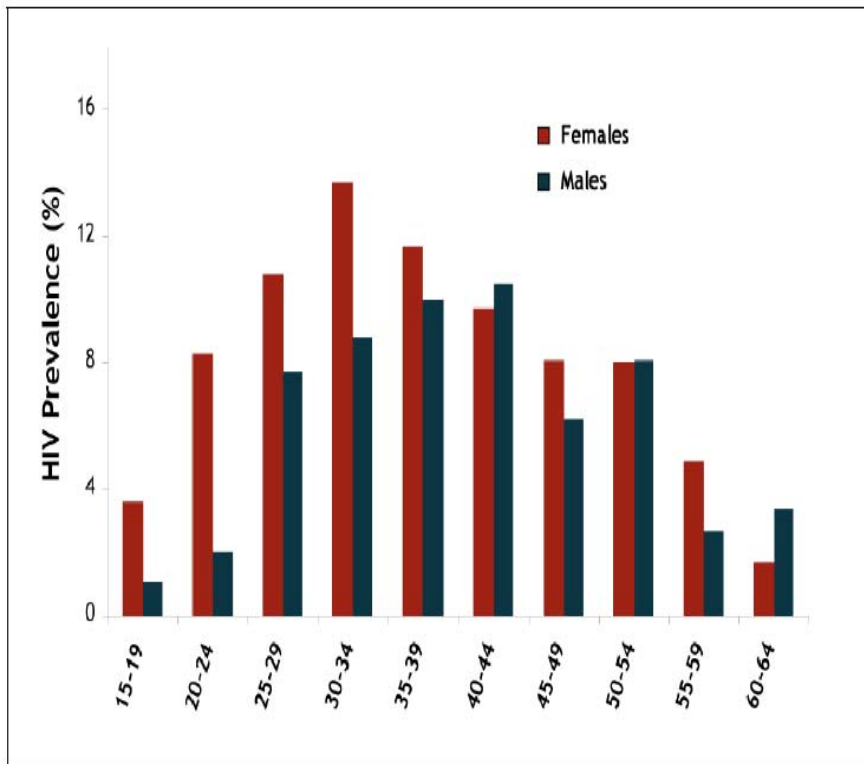
VCT- Voluntary Testing and Counseling

WHO- World Health Organization

FIGURE 1: KAIS 2007

KAIS 2007

Kenya AIDS Indicators Survey



2.0 INTRODUCTION: HIV IN KENYA

Since the first case of HIV in Kenya in 1984, approximately 1.5 million people have died from this disease in the country .According to the Kenya Demographic and Health Survey (KDHS) of 2003, the national prevalence stands at 6.7%. The Kenya AIDS Indicator Survey (KAIS) 2007 estimates HIV prevalence at 7.8%. Treatment is now available in 345 sites countrywide. NASCOP estimates that 213,000 patients are on ARV treatment including adults and children as at March 2009, which is only 50% of those who require HAART.

3.0 HISTORY OF HIV INFECTION 1

The worldwide dissemination of human immunodeficiency virus (HIV) over the past four decades is one of the most catastrophic examples of the emergence, transmission, and propagation of a microbial genome. HIV infection appears to be a zoonosis, with AIDS resulting from the failure of HIV to adapt to a relatively new host, or perhaps a failure of humans to adapt to HIV infection.

The virus has a predilection for activated HIV-specific CD4+ T cells, although other cells are also susceptible to the virus. This tropism for particular cells is determined mainly by cellular receptors to which HIV attaches in order to enter cells.

The earliest documented case of HIV infection in humans was identified in a sample of serum from Kinshasa (Democratic Republic of Congo) that was stored in 1959.²

AIDS was first recognized 1981; in Los Angeles, Gottlieb et al³ reported five previously healthy gay men who developed pneumocystis carinii pneumonia (now pneumocystis jirovecii pneumonia-PCP), while Friedman-Kien et al described Kaposi's sarcoma and PCP in 26 homosexual men in New York⁴ .The first published case in Kenya was documented in 1984 at Kenyatta National Hospital⁵.

4.0 LITERATURE REVIEW

4.1 MECHANISM OF HIV DISEASE

IMMUNOLOGY OF HIV INFECTION

The distinctive feature of HIV infection is the profound loss of CD4+ cells, which accounts for majority of the manifestations of the disease as CD4+ T-cells are fundamental to the development of specific immune responses to infection, particularly intracellular pathogens.

HIV largely infects activated CD4+ cells, causing the activated T-cells directed against the virus to be at greatest risk of infection. The ability of the immune system to mount a specific response against HIV is a key factor in the subsequent disease course. Long-term non-progressors appear to have better lymphoproliferative responses to HIV-specific antigens than those with more rapid progression⁶.

Activated by CD4+ T helper cells, anti-HIV specific CD8+ T-cells have a crucial role to play in the control of viremia, increasing in response to ongoing viral replication.

Substantial depletion of mucosal CD4+ T cells probably occurs in the early stages of acute infection, possibly owing to viral cytopathogenicity and the action of HIV-specific CD8+ T cells. Several events occur that conspire to deplete CD4+ T cells over the protracted, chronic phase of the infection, with predominant infection of memory CD4+ cells. These factors are thought to include chronic activation of T cells, inhibition of thymic output, suppression of the bone marrow, destruction of lymph-node architecture, and low-level ongoing infection of memory CD4+ T cells.

Although it is the sustained immune activation induced by HIV infection that underlies the high rates of proliferation and death of both CD4+ and CD8+ T cells, the pool of

CD4+ T cells, which is already depleted in acute infection, is more vulnerable to the effects of this disrupted homeostasis than CD8 T cells.⁷

A small proportion of the infected cells stop proliferating, entering into a pool of infected quiescent T cells (latent reservoir), thus ensuring lifelong persistence of the virus even with the use HAART.⁸

In humans, the first cells to become infected by HIV may be CD4+ T cells and not dendritic cells,^{9,10} especially within the thin rectal and cervical epithelia. Nevertheless, dendritic cells may play a role in the initial phases of HIV infection because they display a specific cell-surface lectin, dendritic-cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), which captures carbohydrate moieties on the gp120 of HIV and mediates clustering of dendritic cells with T cells.^{11,12} DC-SIGN, which is not expressed by Langerhans cells, appears to act by concentrating virus in dendritic cells or by transmitting bound HIV to CD4+ T cells that express either CXCR4 or CCR5 surface receptors.

Macrophages and their precursors express only low levels of CD4 but abundant levels of heparan sulfate proteoglycans, especially syndecan. Like DC-SIGN, syndecan binds to HIV efficiently and is an important factor in viral dissemination and tropism. Another receptor expressed by macrophages, CD91, binds to heat-shock proteins, including those on the HIV virion membrane¹³. Although macrophages may be a primary target for infection and source of virus production, particularly during opportunistic infections, the longevity of macrophages *in vivo* and their role as a persistently infected long-term reservoir is unclear.

There have been reports of HIV infection of CD8+ T cells, particularly in patients with late-stage disease. These may be explained by the expression of CD4 by activated CD8+ T cells.¹⁵ Studies using high-purity flow-cytometric sorting have shown that the frequency of infected CD8+ memory T cells is very low in patients with HIV infection, but that the cells within this population that express CD4 are preferentially infected.

Natural killer cells, which do not require prior sensitization to recognize and kill targets, express CD4 and can be productively infected by both CXCR4- and CCR5-tropic strains in vitro, and also act as a viral reservoir.

4.2 THE ANATOMICAL HOME OF HIV

LYMPHOID TISSUE

In acute HIV infection, the dominant site of infection is the mucosal and gastrointestinal lymphoid tissue (GALT). These contain at least half of the body's T cells. In studies done on macaques monkeys infected with SIV, almost the entire intestinal CD4+ population is wiped out within three weeks of infection.⁹ It is postulated that a similar phenomenon occurs in humans.

The large loss of mucosal CD4+ T cells so early in the infection suggests that counts of peripheral-blood CD4+ T cells may underestimate the degree of T-cell destruction.

As the infection progresses from the acute phase into the chronic phase, HIV replication begins to include other peripheral lymphoid organs such as dendritic cells, thymus, bone marrow and circulating lymphocytes.

CENTRAL NERVOUS SYSTEM

The capacity of HIV to cause disease in the central nervous system suggests that the virus may persist and replicate there.^{16,17,18} Viral particles have been identified in brain-derived macrophages and microglia and isolated from the cerebrospinal fluid.

In patients with neurologic symptoms associated with AIDS, HIV-specific antibodies have been detected in the cerebrospinal fluid.^{19,20} HIV isolated from cerebrospinal

fluid tends to be more macrophage-tropic than does virus circulating in plasma, and thus HIV replication may be compartmentalized in the central nervous system.^{21,22}

The HIV transactivating factor Tat, which is taken up into neurons by means of CD91 and is thought to exert neurotoxic effects by increasing the production of nitric oxide and interfering with the integrity of the blood-brain barrier.

Due to poor drug penetration of ARVs, the brain acts as a reservoir for HIV even during maximal retroviral suppression.

GENITOURINARY TRACT

HIV replication has been detected in T cells and macrophages present in semen and within the renal epithelium^{23,24}. In situ hybridization of renal-biopsy tissue from patients with HIV nephropathy suggests the presence of a reservoir of HIV, even in patients with undetectable levels of viral RNA in plasma. Similarly, HIV has been detected in macrophages and lymphocytes within the cervix.²⁵

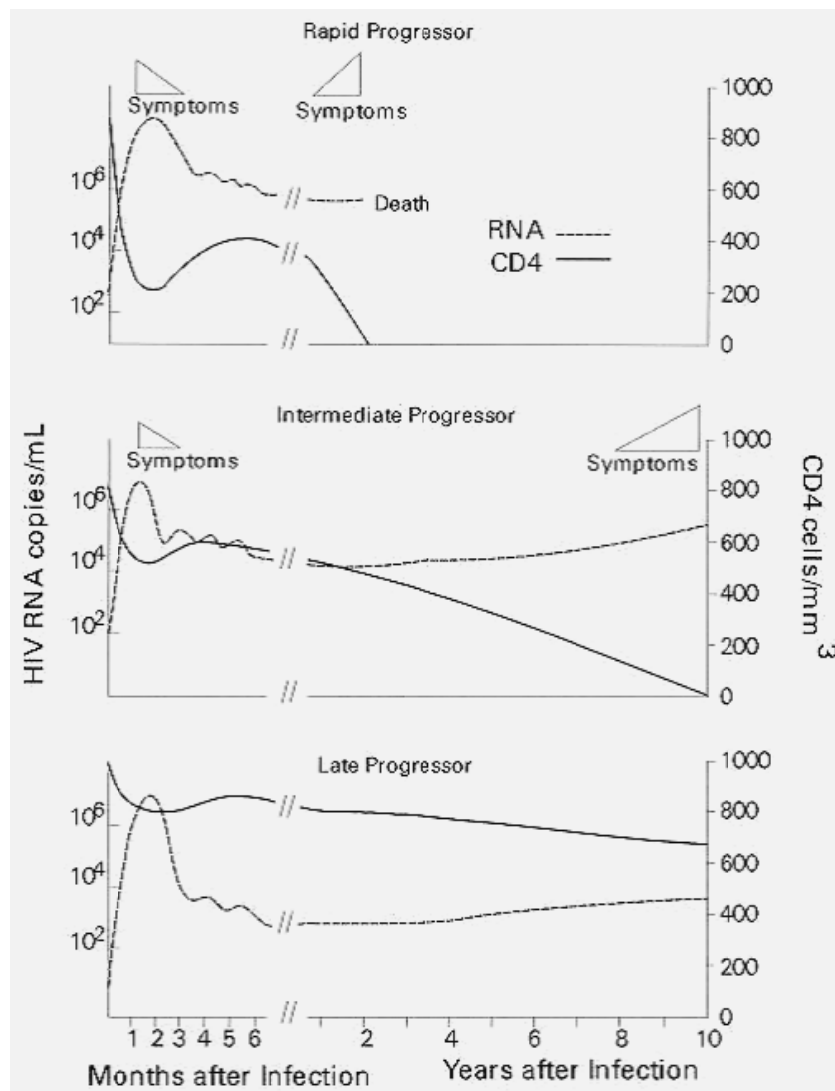
It is unclear whether HIV can become truly latent in the genitourinary tract or whether it merely continues to replicate slowly, impervious to the effects of HAART. These factors clearly affect not only the course of the infection within individual patients, but also the transmission of the virus to sexual partners.

4.3.1 ROLE OF CD4 IN MANIFESTATION OF HIV DISEASE³⁸

Throughout the clinically latent period associated with HIV infection the virus continues to actively replicate, usually resulting in symptomatic illness. Highly variable disease progression rates between individuals are well-recognized, with progression categorized as rapid, typical or intermediate and late or long-term non-progression.

The majority of infected individuals (70%-80%) experience intermediate disease progression in which they have HIVRNA rise, CD4+ T-cell decline and development of AIDS related illnesses within 6-10 years of acquiring HIV. However, 10% to 15% of patients are termed as rapid progressors as they have a fast CD4+ T-cell decline, with development of AIDS within 1-3 years of acquiring HIV infection. The late progressors, who make up 5% of the HIV infected patients, have a very slow CD4 decline despite having the disease for many years. They can remain healthy without significant changes in CD4 count or HIV-RNA for over 10 years.

FIGURE 2: NATURAL HISTORY OF HIV-RNA LEVELS AND CD4 COUNTS AT THREE RATES OF DISEASE PROGRESSION



According to both the World Health Organization (WHO) and the Centre for Disease Control (CDC), any HIV-infected individual with a CD4+ T cell count < 200 cell/ μ L has AIDS by definition, regardless of the presence of symptoms or opportunistic diseases. The CD4+ T-cell count is the most significant predictor of disease progression and survival, and the US Department of Health and Human Services (DHHS) ART treatment guidelines recommends treatment commencement be based on CD4+ T-cell count in preference to any other single marker.

Lower CD4 counts are associated with greater risk of disease progression. CD4 counts from 350-500 cells/mm³ are associated with risks of $\leq 5\%$ across all age and HIV-RNA strata, while the risk of progression to AIDS increases substantially at CD4 counts <350 cells/mm³, the greatest risk increase occurring as CD4 counts fall below 200 cells/mm³. The risk of disease progression at 200 cells/mm³ is generally double the risk at 350 cells/mm³.³²

4.3.2 WHO CLINICAL STAGING^{41,42}

The original WHO clinical staging system for HIV/AIDS, developed in 1990⁴¹, emphasized the use of clinical parameters to guide clinical decision-making for the management of HIV/AIDS patients. It was designed for use in resource limited settings where there was limited access to laboratory services. The WHO clinical staging system has been widely used in resource-limited countries, particularly in the African region, and has proved pragmatic and useful in facilities at both the first level and the referral level.

In the current guidelines of 2005⁴², clinical events are categorized as those where a presumptive clinical diagnosis may be made (conditions that can be diagnosed clinically or with basic laboratory tests) and those where a definitive diagnosis may be made (for conditions requiring more complex and sophisticated laboratory investigations). (See Appendix 4)

4.4 ROLE OF SURROGATE MARKERS IN THE ASSESSMENT OF DISEASE PROGRESSION ³⁸

While CD4 counts and HIVRNA are the gold standard markers for disease monitoring, when measurement of these parameters is not possible surrogate markers become important. Markers investigated for their utility as simple markers for disease progression in resource-limited settings include delayed type hypersensitivity responses, total lymphocyte count, haemoglobin and body mass index (BMI).

DELAYED TYPE HYPERSENSITIVITY REACTION (DTH)

Mediated by CD4+ T-lymphocytes, DTH-type responses give an indication of CD4+ T-cell function in vivo. It has been shown that DTH responses decline with the fall of CD4+ T-cells resulting in a corresponding increase in mortality. Failure to respond to a given number of antigens has been suggested as a marker for the initiation of ART in resource-limited settings. ^{33,34}

BODY MASS INDEX

BMI relationship to survival in HIV infection is important for two main reasons: Firstly, 'wasting syndrome' (>10% involuntary weight loss in conjunction with chronic diarrhoea and weakness, +/- fever) is considered an AIDS defining illness according to the WHO and CDC classifications. Secondly, the ease of measurement of this parameter makes it potentially highly useful as a marker for the initiation and monitoring of ART in resource limited countries.

In a study carried out in France, a rapid decline in weight was noted in the 6 months preceding AIDS although the sensitivity of this measure was only 33%. A baseline BMI of <20.3 kg/m² for men and <18.5 kg/m² for women is predictive of increased mortality, even in racially diverse cohorts, with a BMI of 17-18 kg/m² and <16 kg/m²

being associated with a 2-fold and 5-fold risk of AIDS respectively.³⁵ A BMI of <18.5 kg/m² was consistently strongly associated with increased risk of disease progression and may prove to be a valuable indicator of the need for HAART.³⁶

TOTAL LYMPHOCYTE COUNT

WHO guidelines recommend using total lymphocyte count of 1200 cells/mm³ or below as a substitute marker for CD4 count for ART initiation in symptomatic HIV positive patients.

HAEMOGLOBIN

Haemoglobin levels reflect rapidity of disease progression rates and independently predict prognosis across demographically diverse cohort. Rates of haemoglobin decrease also correlate with falling CD4 counts.

4.5 USE OF WHO CLINICAL STAGING AS A SURROGATE OF CD4+ COUNT

The WHO clinical staging can be used as the single criterion to commence HAART in resource poor settings where CD4 count is unavailable. However, it has various shortcomings which make it a poor alternative to CD4 and viral load monitoring. Clinical acumen varies from one clinician to another depending on level of training. In resource poor settings, lack of well equipped laboratory and radiological services may result in misdiagnosis of the patient and subsequent improper staging. Concurrent illness such as diabetes, malignancies and malnutrition may alter the clinical presentation of the patient; such as weight loss and development of illnesses such as TB.

According to the interim WHO 2005 clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance (African region)⁴² the level of immunosuppression is classified according to the CD4 count as shown.

TABLE 1: CD4 LEVELS IN RELATION TO THE SEVERITY OF IMMUNOSUPPRESSION

Not significant immunosuppression	>500/mm ³
Mild immunosuppression	350 - 499/mm ³
Advanced immunosuppression	200 - 349 /mm ³
Severe immunosuppression	<200/mm ³

In a study by Kaagayi et al²⁶ in Rakai district in Uganda, the ability of WHO clinical staging to predict CD4 cell counts of 200 cells/ μ l or less was evaluated among 1221 patients screened for antiretroviral therapy (ART). 929 (76%) of the patients were in stage 1 or 2 whereas 292 (24%) were either in stage 3 or 4. Sensitivity was 51% and specificity was 88%. The positive predictive value was 64% and the negative predictive value was 81%. 49% of patients with CD4 count <200 were classified as WHO stage I or II while 12% who had stage III or IV also had CD4 count >200. Clinical criteria missed half the patients with CD4 cell counts of 200 cells/ μ l or less, highlighting the importance of CD4 cell measurements for the scale-up of ART provision in resource-limited settings.

Table 2: Ability of WHO Clinical Staging to predict CD4 T cell count of 200 cells/ μ l

	>200 (857)	<200(364)
WHO Stage I/II (929)	751	178
WHO Stage III/IV (292)	106	186

In a similar study carried out by Jaffar et al²⁷ in Jinja Uganda, assessed the ability of the WHO clinical stage to accurately identify HIV-infected patients who require HAART. Among 4302 subjects screened for ART, 2254 (52%) had CD4 count < 200 \times 10⁶/l of whom 1091 (48%, 95% CI 46, 50%) were classified at WHO stage I or II. The

sensitivity and specificity (95% CI) of WHO stage III or IV against a CD4 count of $<200 \times 10^6/l$ were 52% (50-54%) and 68% (66-70%) respectively.

Table 3: Ability of WHO Clinical Staging to predict CD4 T cell counts of 200 cells/ μ l

	CD4 >200 (2048)	CD4< 200(2254)
STAGE 1 OR 2 (2491)	1400	1091
STAGE 3 OR 4 (1811)	648	1163

Plasma viral load was tested in a subset of 1453 subjects in whom ART was initiated. Among 938 subjects with plasma viral load of 100,000 copies or more, 391 (42%, 95% CI 39, 45%) were at WHO stage I or II. 45% of subjects with CD4 count $\geq 200 \text{ cells} \times 10^6/l$ had plasma viral load of 100,000. In these subset of patients, HAART should be initiated to reduce infectivity and progression of disease. The median (IQR) CD4+ counts and plasma viral loads were 109 (35, 165) $\times 10^6/l$ and 163200 (63600, 370400) copies per ml respectively.

This study highlighted the large number of patients (48%) who could have been denied HAART if only assessed on the basis of WHO clinical staging. In 42% of patients in WHO stage I or II , qualified for HAART on basis of CD4+ had viral load $>100,000$. The prohibitive cost of viral load assessment prevents it from be used routinely in resource poor settings despite its utility in guiding the initiation of HAART.

A study done in Nigeria by Onyemelukwe et al ²⁸, comparison of CD4+ in 80 HIV positive patients against 40 HIV negative controls matched for age and sex showed a mean CD4+ cell count of 240 cells $-/+ 170$ and 600 cell $-/+ 170$ respectively ($p < 0.05$)

Torpey et al ²⁹ carried out a retrospective study carried out in Ghana from 2002 to 2005 involving 5784 patients enrolled in an HIV treatment programme in two urban and two rural sites. Of the patients, 29.5% were in clinical Stages I and II and had a CD4+ lymphocyte count less than 200 cells/mm³. Of Stage I and II patients, 34.6% had a CD4+ T-lymphocyte count less than 350 cells/mm³. Of patients with counts less than

200, 70.4% were in Stages III and IV and were eligible for treatment. In all, 40.7% and 29.1% of the patients with counts of more than 200 and 350 cells/mm³ , respectively, were in Stage III or IV.

In a study carried out in India by Sharma et al ³⁰ involving 135 inpatients, fever and weight loss were the commonest presenting symptoms (71% and 65% respectively). Tuberculosis was the commonest OI (71%) followed by candidiasis (39.3%), *Pneumocystis jiroveci* pneumonia (7.4%), cryptococcal meningitis and cerebral toxoplasmosis (3.7% each).

A retrospective study carried out in Saudi Arabia by Edathoju et al ³⁷ involving 191 patients showed a correlation between WHO clinical staging and CD4 count. The distribution of patients at the WHO clinical stages was 110 for stage 1, 10 at stage 2, 36 at stage 3, and 35 at stage 4. Mean CD4+ T-lymphocyte counts were 457, 337, 188, and 86/mm³ at the respective stages. The difference between the mean CD4+ T-lymphocyte count in patients at stage IV and at each of the other stages was significant; p<0.0001. The Spearman correlation between the stages and the mean CD4+ T-lymphocyte counts was -0.65.

Table 4: WHO Clinical Staging and Mean CD4 T cell count

	MEAN CD4 COUNT (cells/μl)
STAGE 1 (110)	457
STAGE 2 (10)	337
STAGE 3 (36)	188
STAGE 4 (35)	86

In a cohort study done in Addis Ababa by Kassa et al ³⁸ involving 86 patients, the median CD4 count was 337, 262, 225, 126, and 78 (P< 0.01) with clinical stage of HIV infection (1, 2, 3 cohort, 3 hospital, and 4, respectively).

Table 5: WHO Clinical Staging and Median CD4 T cell count

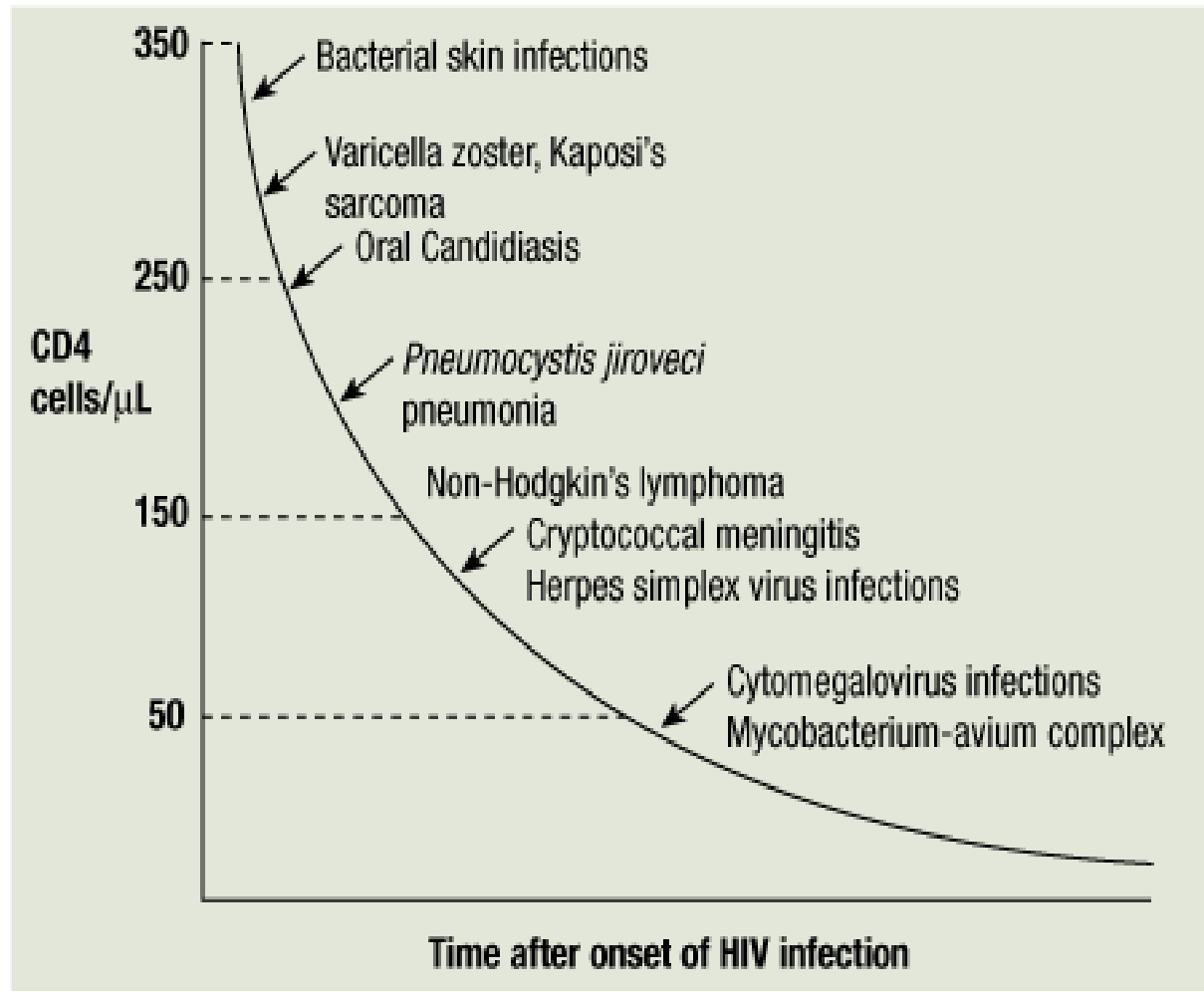
	MEDIAN CD4 COUNT (cells/ μ l)
STAGE 1 (53)	337
STAGE 2 (16)	262
STAGE 3- OUTPATIENT (1)	225
STAGE 3- HOSPITAL (15)	126
STAGE 4 (1)	78

A retrospective study carried out in Cambodia by Huyst et al³⁹, involving 648 patients, the WHO 2003 clinical criteria had a sensitivity of 96%, a specificity of 57% to identify patients who required HAART.

In a study at KNH by Odhiambo in 2008³¹, normal chest radiographs were more common in TB culture positive HIV positive patients compared to TB culture positive HIV-negative patients ($p= 0.048$) . 9 (7%) of patients who had normal chest radiographs had positive sputum cultures.

Few trained medical personnel such a radiologists to interpret chest radiographs in suspected PTB cases and unavailability of sputum culture has led to misdiagnosis of TB especially in HIV patients. PTB in HIV usually presents atypically, with less cavitations, more intrathoracic adenopathy and millary pattern.³¹

FIGURE 3:MANIFESTATION OF OPPORTUNISTIC INFECTIONS WITH FALL IN CD 4 COUNTS



5.0 STUDY JUSTIFICATION

Although CD4 T cell count is considered to be the most important determinant of commencement of HAART, it is not readily available in resource poor settings. With only 50% of HIV patients in need of HAART are already on treatment, the Ministry of Health in conjunction with WHO are rapidly scaling up the provision of antiretroviral drugs in the country. In Kenya, WHO Clinical Staging alone can be used in cases where CD4 is unavailable both for initiation of HAART and as well as monitoring of treatment. Many HIV care and treatment centers lack CD4 testing services and therefore base the management of patients on the clinical stage.

The WHO Clinical Staging was a tool designed to be used with, or in the absence of CD4 T cell counts. Its clinical utility has been studied in various countries but no studies have been published in Kenya to date. This study aims to determine the clinical utility and accuracy of the WHO Clinical Staging to correctly stratify the patients according their CD4 T cell counts at Kenyatta National Hospital.

5.1 RESEARCH QUESTION:

What is the degree of correlation between WHO clinical staging and CD4 count at KNH?

6.0 STUDY OBJECTIVES:

General objective:

- To determine the association of CD4 T cell counts with WHO clinical staging in HAART-naïve patients at KNH.

Specific objectives:

- To determine the clinical and immunologic characteristics of HIV patients at KNH.

- To determine the degree of correlation between CD4 T cell count and WHO clinical staging of HIV patients at KNH.

7.0 METHODOLOGY

Site for the study:

Kenyatta National Hospital

Study population/ Case definition:

Newly diagnosed HIV positive patients by either two ELISA or two rapid tests (Unigold and Determine).

Study design:

Cross sectional study

Inclusion criteria:

Age 18- 49 years

HIV positive patients confirmed by ELISA or rapid test

Naïve to HAART

Have given written informed consent

Exclusion criteria:

Patients with prior CD4 T cell counts done

Patients on cotrimoxazole prophylaxis

Patients on immunosuppressive agents e.g steroids, cytotoxic drugs

Patients with concurrent immunosuppressive illnesses e.g Diabeted Mellitus ,non-HIV associated malignancies.

Pregnant women

7.1.1 SAMPLE SIZE CALCULATION

Sample size calculation in a cross sectional study is based on the assumption that the test that estimates this proportion is perfectly sensitive and specific. The sample size is calculated from the previous studies, using the highest specificity (Rakai Study-88%) and lowest specificity (Cambodia Study- 57%).

Estimation of sample size for testing Ho: $p_1 = p_2$

Assumptions:

alpha = 0.05

power = 0.8

$$N = \frac{[Z_{\alpha} \sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta} \sqrt{P_C(1-P_C) + P_T(1-P_T)}]^2}{\Delta^2}$$

P_i = Proportion from Rakai study

P_C = Proportion from Cambodia study

N = Sample size

Z_{∞} - Constant associated with ∞ . For $\infty = 0.05$, $Z_{\infty} = 1.96$

Z_{β} - Constant associated with β . For $\beta = 0.80$, $Z_{\beta} = 0.84$

-

\bar{p} - $(P_C + P_T) / 2$ (Average proportion)

$\Delta = P_T - P_C$ (Difference between the proportions).

N = 76

7.1.2 SAMPLING

Recruitment from both inpatients and outpatients was done in order to obtain representative samples of all the clinical stages with majority of Stage 1 and 2 projected to be derived from the outpatient clinic and stage 3 and 4 for mainly from the inpatients. An equal number of patients were recruited in both the inpatients and

outpatients. Consecutive sampling was carried out until the desired sample size was achieved.

76 in-patients + 76 out-patients= 152

7.2 RECRUITMENT OF PATIENTS

The comprehensive care clinic, which is the KNH outpatient HIV clinic, runs from Monday to Friday from 8am to 5pm. The principle investigator perused all the new files at the records department. Patients who satisfied the inclusion criteria and agreed to participate in the study by signing an informed consent were recruited into the study. Patients who were on HAART or on cotrimoxazole prophylaxis or declined to be give consent were excluded. Patients with CD4 counts already done were also excluded to prevent observer bias. Patients were also excluded if they were diabetic, were on immunosuppressants such as steroids, had a non-HIV associated malignancy or were pregnant.

Outpatients recruited were mainly from VCT (voluntary counseling and testing) centres. 70 patients (92.1%) were from VCT, while 6 patients (7.9%) were referred to CCC from medical outpatient clinics and the accident and emergency centre.

Kenyatta National Hospital (KNH) has 8 general and specialist medical inpatient wards. Each ward has one day a week for admissions. With the current initiative by the Ministry of Health to scale up diagnosis of HIV, provider initiated counseling and testing (PITC) is proved to all patients presenting to A& E, specialist consultation clinics and inpatient wards. The principle investigator, together with a study assistant, went to the medical ward that had admitted patients in the previous 24 hours. Patients were recruited if they tested HIV positive during the current admission/ illness, either from tests done in the ward or from the referring health facility if they were referred to KNH. Patients on cotrimoxazole prophylaxis prior to recruitment, with CD4 counts already performed, or declined to give consent were excluded from the study.

Patients were evaluated using the screening profoma (See Appendix 3). Additional information was derived from the patients' file and treatment sheets. Auxiliary

investigations that were required for staging of the patient were carried out, with the cost being borne by the principle investigator. All radiographs, CT scans and other radiological tests were analyzed and reported by two radiologists, each reviewing the films independently.

7.3 CLINICAL METHODS

The principle investigator administered all the questionnaires so as to remove inter-observer bias. Patient characteristics were entered into the screening profoma (See Appendix 3). Auxillary tests such as Chest radiographs, biopsies and sputum examinations were carried out when required for purposes of clinical staging. The clinical staging was determined using the WHO 2005 clinical staging for adults and adolescents: Presumptive and definitive criteria for recognizing HIV/AIDS related clinical events (See Appendix 5).

Patients were briefed on their results of their physical and laboratory examinations, counseled appropriately and given the necessary treatment for their opportunistic infections. All the information was duplicated into the patient's file so as to enable patient follow up in subsequent visits. Blood was drawn for CD4 count and submitted to the laboratory within 3 hours of venesection. The results of the CD4 counts became available to the principle investigator at least one or two days after examination for outpatients and three to four days for inpatients. The results from the clinical staging and CD4 count were communicated both to the patient and the primary doctors, as well as being documented in the patient's file. This was done to ensure proper management of the patient.

7.4 LABORATORY AND RADIOLOGICAL METHODS

Blood (3mls) was obtained from the antecubital fossa and transported to the laboratory in EDTA bottle for determination of level of CD4 count using Partec Cytoflow method. (See Appendix 4)

Other investigations were carried out if they were required to make a clinical diagnosis and to follow up on treatment. Examples include a lumbar puncture performed in a patient with signs and symptoms of meningitis, histology for kaposi's sarcoma; liver function tests, urea, electrolytes and creatinine to monitor adverse drug events.

The recommended procedures for specimen collection, proper labeling and storage was adhered to minimize errors.

Radiographs done as part of the diagnostic work up were reviewed by two consultant radiologists separately.

7.5 DATA ANALYSIS

The data was collected, verified and entered into a password protected computer database. Analysis of the data was carried using Statistical Package for Social Scientists (SPSS) version 17.0

The data obtained was categorised as either continuous or categorical. Continuous variables were age and CD4 T cell counts. Categorical variables were opportunistic infections, WHO clinical stage, radiologic findings, gender, marital status, education level, occupation and mode of HIV diagnosis.

Continuous data was described using counts, mean, median and 95% confidence intervals. Categorical variables were described using counts and proportions.

The age, gender, marital status, occupation, opportunistic infections and radiologic findings were presented in form of tables. The WHO clinical staging and CD4 T cell counts were presented in form of tables and graphs. Differences in CD4 T cell counts were analyzed using the student T-test. Association between CD4 and WHO clinical staging was done using univariate analysis.

The student t-test was used to analyze the CD4 T cell counts and age. The chi-square was used to analyze proportions in the categorical variables such as WHO clinical staging and gender.

The clinical utility of the WHO clinical staging to accurately predict CD4 of 200cells/ μ l and 350cell/ μ l count was done using two by two tables. These were used to calculate the sensitivity, specificity, negative predictive value and positive predictive value.

Correlation between the WHO clinical staging and the CD4 T cell counts was carried out using spearman's rank correlation coefficient.

P values calculated reported were two-tailed and were deemed significant if

$p \leq 0.05$

8 .0 ETHICAL CONSIDERATIONS

1. Permission to carry out the study was sought and obtained from the Kenyatta National Hospital/ University of Nairobi Scientific and Ethical Review Committee.
2. Patients were enrolled into the study after giving an informed written consent.
3. Standard evaluation and care was given to all the patients.
4. Results of the clinical evaluation, laboratory and radiological investigations were communicated to the patients as well as the primary health care providers to ensure proper management of the patients.
5. Those that declined to give consent were not discriminated upon.
6. Confidentiality for each client was maintained.

9.0 RESULTS

The study was carried out between April 2010 and February 2011, whereby a total of 282 patients were evaluated for inclusion into the study. 130 patients were excluded from the final analysis as shown in the flowchart. Missing data exclusion was used to handle missing data required for the final analysis; in this case CD4 T cell count and laboratory investigations required to stage the patients. More patients were recruited to replace the ones with incomplete data. The final analysis was carried out in 152 patients.

FIGURE 4: RECRUITMENT FLOW CHART OF THE PATIENTS

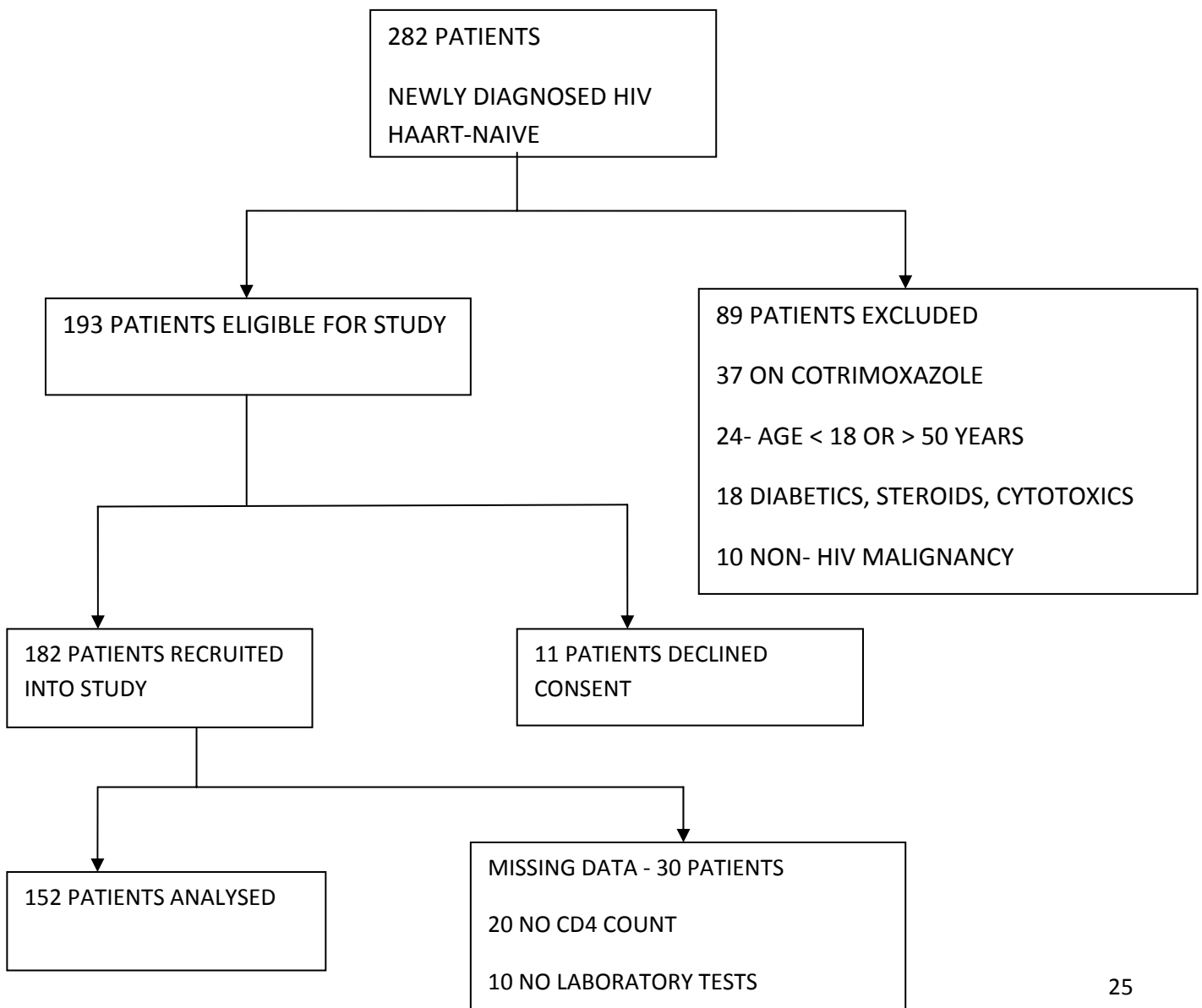


TABLE 6 SHOWING SOCIO-DEMOGRAPHIC PROFILE OF THE PATIENTS (N=152)

SOCIO-DEMOGRAPHI CHARACTERISTICS	ALL PATIENTS (N=152)
AGE –YEARS \pm 2SD	35.25 \pm 1.71
FEMALE SEX-NO (%)	80(52.6)
MARITAL STATUS-MARRIED-NO (%)	100 (65.1)
EDUCATION PRIMARY AND BELOW-NO (%)	71 (46.7)
EDUCATION SECONDARY AND ABOVE-NO (%)	81 (53.3)
OCCUPATION EMPLOYED-NO (%)	87 (57.2%)
MODE OF HIV DIAGNOSIS (VCT)-NO (%)	70 (46.1)
MODE OF HIV DIAGNOSIS (PITC)-NO (%)	82(53.9%)

The mean age of the study group was 35.25 years with a female predominance of 52.6%.

65% of the patients were married with 53.3% having attained at least high education.

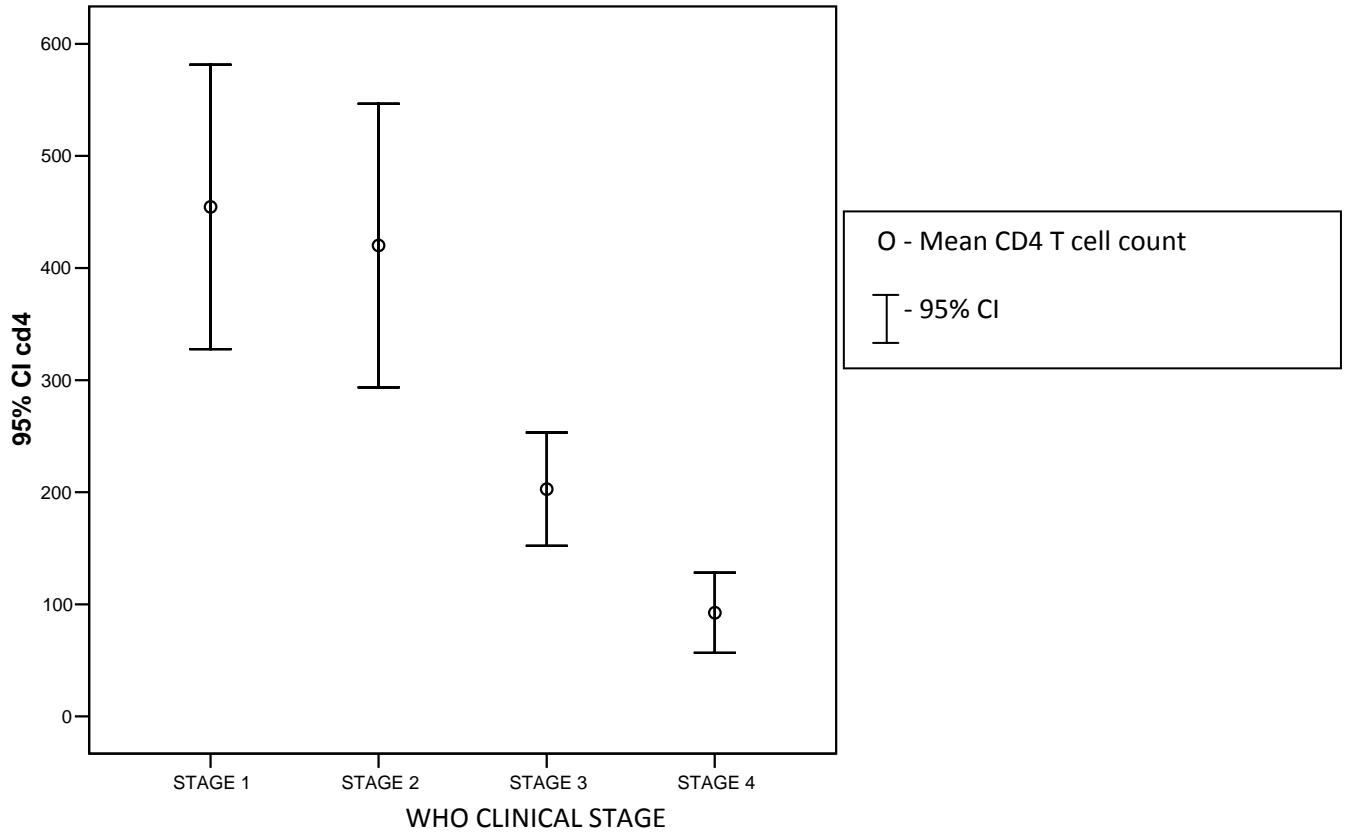
TABLE 7 COMPARING CLINICAL STAGING AND CD4 COUNT DIFFERENCE IN ALL THE PATIENTS (N=152)

	MEAN CD4 COUNT	MEDIAN CD4 COUNT	95% CI	WHO CD4 COUNT RANGE
STAGE 1 (26)	455	388	334- 575	>500
STAGE 2 (19)	420	347	302- 538	350- 499
STAGE 3 (59)	203	140	153- 252	200- 349
STAGE 4 (48)	92	44	58- 127	<200
ALL STAGES (152)	238	158	198- 278	-

The mean CD4 count in Stage 1 of 455 was lower than expected from the WHO value of 500. The mean CD4 count in Stage 2 ,3 and 4 correlated with WHO values.

Spearman's correlation coefficient between the WHO clinical staging and CD4 count was -0.583 with a drop in the CD4 count with each advancing WHO clinical stage.

FIGURE 6 SHOWING CLINICAL STAGING AND CD4 COUNTS IN ALL THE PATIENTS(N=152)



The 95 % confidence interval (334-575) in WHO stage 1 was lower than expected WHO counts of more than 500 cells/ μ l.

The 95 % confidence interval in WHO Stages 2, 3 and 4 was comparable to the expected WHO counts.

TABLE 8 SHOWING SENSITIVITY AND SPECIFICITY OF CLINICAL STAGING TO PREDICT CD4 COUNTS OF 200

	CD4 >200	CD4< 200
WHO STAGE 1&2	36	9
WHO STAGE 3&4	31	76

The sensitivity of the WHO clinical staging to predict CD4 T cell counts of 200 cells/ μ l was 53% with specificity of 89%. The positive predictive value was 80% and the negative predictive value was 71%

TABLE 9 SHOWING SENSITIVITY AND SPECIFICITY OF CLINICAL STAGING TO PREDICT CD4 COUNTS OF 350

	CD4 >350	CD4< 350
WHO STAGE 1&2	24	21
WHO STAGE 3&4	14	93

The sensitivity of the WHO clinical staging to predict CD4 T cell counts of 350 cell/ μ l was 63% with specificity of 82%. The positive predictive value was 53% and the negative predictive value was 87%.

TABLE 10 SHOWING PREVALENCE OF HIV CLINICAL EVENTS IN THE STUDY POPULATION (N=152)

HIV CLINICAL EVENTS	NUMBER OF PATIENTS (%)
Asymptomatic/ PGL	26 (17.1%)
Papular pruritic eruptions	22 (14.5%)
Moderate weight loss <10%	13 (8.6%)
Herpes zoster	10 (6.6%)
Fungal nail infections of the fingers	3 (2.0%)
Angular chelitis	2 (1.3%)
Seborrhoeic dermatitis	1 (0.7%)
Severe weight loss >10%	43 (28.3%)
Bacterial infections	51 (33.6%)
Bacterial infection (Pneumonia)	28 (18.4%)
Bacterial infection (Meningitis)	10 (6.6%)
Bacterial infection(e.g septicaemia, pyomyositis, UTI)	13 (8.6%)
Pulmonary Tuberculosis	18 (11.8%)
Oral thrush	18 (11.8%)
Chronic gastroenteritis	3 (2.0%)
Oral hairy leukoplakia	2 (1.3%)
Extrapulmonary Tuberculosis	23 (15.1%)
Cryptococcal meningitis	8 (5.3%)
HIV wasting syndrome	4 (2.6%)
Esophageal candidiasis	4 (2.6%)
Chronic herpes simplex infection	3 (2.0%)
HIV encephalopathy	3 (2.6%)
Pneumocystis jiroveci pneumonia	2 (1.3%)
Kaposi's sarcoma	2 (1.3%)
Cerebral toxoplasmosis	2 (1.3%)

HIV CLINICAL EVENTS	NUMBER OF PATIENTS (N=152)
Invasive cancer of the cervix	1 (0.7%)
CMV retinitis	1 (0.7%)

Majority of the patients presented with one or more HIV clinical events.

The most prevalent HIV clinical events were bacterial infections (34%), severe weight loss(28%) and Tuberculosis(27%).

In the majority of the cases, these were clinical impressions and histopathological proof was lacking.

TABLE 11 SHOWING CHEST RADIOGRAPH FINDINGS (N= 40)

RADIOGRAPHIC DIAGNOSIS	NUMBER
Pulmonary Tuberculosis	15
Miliary Tuberculosis/ TB pleural effusion	7
Bacterial pneumonia	3
Normal chest radiographs	13
Normal chest radiograph with sputum positive for AAFBs	2

These were chest radiograph reports of the patients who presented with symptoms of pulmonary disease as reported by two radiologists independently. Their reports were concordant in 90% of the radiological films reported.

10. DISCUSSION

This study was undertaken to try and establish the degree of correlation between the WHO clinical staging and CD4 T-cell count in newly diagnosed adult HIV/AIDS patients presenting to the Kenyatta National Hospital.

The WHO clinical staging is a tool developed to be used in resource constrained settings where facilities for CD4 count may not be readily available. The Original WHO clinical staging was published in 1990⁴¹ after observations that certain opportunistic infections occurred at a specific CD4 T-cell count (See Appendix 7). This study was carried out using the interim WHO 2005 clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance (African region).⁴²

In this study, 152 newly diagnosed HIV patients either by rapid test or Elisa method were recruited. The mean duration of HIV diagnosis at recruitment was 9 days. Patients recruited into the study were HAART-naïve and had never used cotrimoxazole prophylaxis.

The overall sex distribution in this study was 52.6% females and 47.4% males with a mean age of 35.25 years. Studies carried out in the comprehensive care centre (CCC) have shown a higher female preponderance. In a study carried out by Mwita⁴³ who looked at prevalence and correlates of anaemia at the CCC, 61.8% of the patients in the study were female. A study carried out by Gitura⁴⁴ who looked at the utility of total lymphocyte count as a surrogate marker for CD4 T cell counts in the initiation of HAART at the CCC found that females made up 65.8% of the study patients. Ogoni⁴⁵ who looked at thrombocytopenia in HAART naïve patients at CCC also found females made up 61.6% of the study population.

The Kenya 2009 Population and Housing Census⁴⁶ showed that Nairobi province had a male to female ratio of 1.04:1, whereas the Kenya Demographic and Health Survey (KDHS) of 2003⁴⁷ showed that in every province, women were more likely to be tested

than men. The Kenya AIDS Indicator Survey (KAIS) 2007⁴⁸ and the KDHS 2008⁴⁹ also found higher HIV testing amongst females.

The higher rate of HIV female patients in this study may be a reflection of more females being tested for HIV. Although this study showed higher rates of females as compared to males, the difference was smaller compared to other studies carried out. The KAIS 2007⁴⁸ report found that in the age groups of 17-19 years and 20-24 years, females were infected disproportionately more than males as compared to any other age groups (See Table 1). Our study was designed to recruit patients age 18-49, although the youngest patient captured in our series was 22 years. Thus, by capturing a slightly older population, we may have excluded more females than male patients.

The commonest HIV clinical events in this study were bacterial infection occurred in 51 patients (33.6%) and severe weight loss which occurred in 43 patients (28.3%). Tuberculosis (TB); both pulmonary and extrapulmonary, was the third commonest clinical event and was diagnosed in 41 patients (27.0%). The high incidence of TB in the study population is in keeping with the national and global estimates. According to National AIDS/STD Control Program (NAS COP) and the National Tuberculosis and Leprosy Program, TB is the commonest opportunistic infection in persons living with HIV/AIDS and accounts for a third of all AIDS related deaths. WHO estimates that one in four HIV deaths in 2009 were due to TB. Sharma et al³⁰, in a study of 135 patients carried out in India found the commonest clinical presentation to be weight loss (65%) with the commonest opportunistic infection being TB (71%).

In the patients who had chest radiographs done as part of the workup for the illness, 22 had a radiologic diagnosis of TB (55%) while 3 patients had features of pneumonia (7.5%). Thirteen patients (33%) had chest radiographs reported as normal despite having symptoms of respiratory disease. Two patients (5%) had no radiological evidence of pulmonary TB despite having sputum positive for AAFBs. Odhiambo³¹ who was looking at the validity of clinical symptoms and chest radiographs in predicting pulmonary TB at KNH found that normal chest radiographs were more common in TB

culture positive HIV positive patients compared to TB culture positive HIV-negative patients ($p= 0.048$). This underscores the role HIV plays in attenuating the clinical presentation of pulmonary TB, making it present more atypically and thus may be missed in the HIV infected patients.

In the study population, 70.4% of the patients presented in stage 3 or 4 with only 29.6% of the patients having clinical stage 1 or 2 disease at the time of diagnosis of their HIV disease. This is in contrast to other studies done which found majority of the patients to be in WHO clinical stage 1 and 2. (See tables 1, 2, 3 ,4).^{26,27,37,38}

Similarly, 75% of the patients in our series presented with CD4 T-cell counts of 350 cells/ μ l or less with 56% having CD4 counts less than 200 cells/ μ l. Overall, over 70% of our patients qualified for HAART from the very onset based either on their CD4 cell count or the WHO clinical stage and were in urgent need for commencement of HAART. This is despite the availability of free VCT services countrywide. According to NASCOP, there are 156 registered VCTs in Nairobi and 952 countrywide⁵⁰. The KAIS 2007⁴⁸ report showed that 83% of HIV-infected people were unaware of their status. This may be an indication that the majority of HIV infected persons are diagnosed with HIV after they develop symptomatic and advanced disease.

The overall mean CD4 T-cell count of 455 for Stage 1, 420 for Stage 2, 203 for Stage 3 and 92 for Stage 4. This correlates to the WHO expected figures in WHO Stages 2, 3 and 4. However, the mean CD4 T cell count in WHO Stage 1 was lower than the expected cutoff of 500 cell/ μ l (See Table 1). Spearman's correlation coefficient was inversely significant ($r= -0.583$) thus demonstrating that there was a decline in CD4 T cell counts with advancement in the WHO clinical stage. The results obtained in this study are also comparable to other studies carried out by Edathoju et al in Saudi Arabia³⁷ and Kassa et al in Addis Ababa who demonstrated good correlation between the CD4 T cell count and the expected WHO cutoffs.³⁸ (See Table 2, Table 4).

In this study 21 (14%) of the patients with clinical stage 1 and 2 had CD4 counts below 200 cells/ μ l; of these, 12 (8%) had CD4 counts between 200 and 350 cells/ μ l, while 9 (6%) had CD4 counts below 200 cells/ μ l. Thus if treatment was delayed on the basis of the WHO clinical staging alone, the risk of developing severe opportunistic infections or dying was twice as likely in the 9 patients with CD4 counts less than 200 cells/ μ l as compared to the 12 patients with CD4 counts between 200 and 350 cells/ μ l. Wilkin et al⁵¹ demonstrated that the optimal time for initiation of HAART was when CD4 T cell counts fell to below 350 cells/ μ l in order to prevent both HIV-related as well as non-HIV-related clinical events. A similar study carried out by Kaplan et al⁵² showed that the risk of opportunistic infections or death was twice as high in patients initiated on HAART at CD4 counts of 50-199 cells/ μ l (Hazard ratio 3.5) as compared to CD4 counts of 200-350 cells/ μ l (Hazard ratio 1.7) in comparison to patients with CD4 counts of greater than 500 cells/ μ l.

In this study, the WHO clinical stage had a sensitivity of 63% in correctly predicting CD4 counts greater than 350 cells/ μ l and specificity of 82% in identifying patients with CD4 counts less than 350 cells/ μ l. A similar study carried out at Makerere University in Kampala by Baveewo et al⁵³ found that in WHO Clinical Stage 1 and 2, the sensitivity to predict CD4 T cell counts of 350 cells/ μ l was only 49.1%. These studies underscore the need for CD4 testing in these patients in order to correctly identify patients in need of HAART despite being in clinical stage 1 and 2. The high specificity in our study demonstrates that patients presenting with severe symptomatic disease are likely to have a low CD4 count. This demonstrates that if the clinical staging was used to identify stage 3 and 4 patients in need of HAART, majority (87%) of the patients would be correctly identified. However, the current WHO guidelines recommend HAART initiation in clinical stage 3 and 4 irrespective of CD4 counts and as such, these patients with CD4 counts greater than 350 cells/ μ l qualify for initiation of HAART.

Using the previous WHO cutoff for initiation of HAART of 200 cells/ μ l, our study had a sensitivity of 53% and specificity of 89%. Similar results were reported in other studies.^{26,27} Kaagayi et al²⁶ found a sensitivity 51% and specificity of 88% with CD4 cutoffs of 200 cells/ μ l. In a study by Jaffar et al²⁷ sensitivity was 52% and specificity

68% of the clinical staging to predict CD4 counts of 200cells/ μ l. (See Table 1, Table 2). In a study carried out in Thailand by Costello et al⁵⁴ the WHO clinical staging criteria had a sensitivity of 33% in identifying patients with CD4 counts of 200cells/ μ l. A similar study carried out in Tanzania by Morpeth et al⁵⁵ had a higher sensitivity of 75% but a low specificity of 36%. These studies demonstrate very low sensitivity and miss nearly half of the patients in need of HAART if the previous cutoff of 200 cells/ μ l is used.

By increasing the cutoff for HAART from 200 cells/ μ l to 350 cells/ μ l, the sensitivity of our study increased from 53% to 63% with a slight decline of specificity from 89% to 82%. Thus, the WHO clinical staging has become a more relevant tool in identifying patients in need of HAART with the use of the current guidelines of 350 cells/ μ l as compared to the previous guidelines of 200 cells/ μ l. This will enable more patients to be correctly identified for initiation of HAART if CD4 counts are lacking.

This study demonstrated that in HIV/AIDS patients presenting to KNH, there was correlation between the WHO clinical stage and expected CD4 T-cell count. Moreover, the WHO clinical staging had a high specificity and was able to correctly identify 82% of patients with CD4 counts of less than 350cells/ μ l. However, the sensitivity was low and missed 37% of patients with CD4 T-cell count of less than 350 cells/ μ l. These results are comparable to studies done elsewhere which demonstrate the low sensitivity of the WHO clinical staging.^{26,27,29,53,54,55}

11.0 LIMITATIONS

- This was a hospital based study, and the results obtained may not be applicable to the general community.
- Viral load was not done as part of the initial workup due to financial constraints.
- Consecutive sampling was carried out and as such the results of this study cannot be inferred to the general population.
- Missing data exclusion that was used to handle missing data might have altered the power of the study.
- The diagnosis of some of the diseases required sophisticated laboratory and radiological facilities; for example the diagnosis of cryptococcal meningitis would require culture of cerebral spinal fluid and thus may have been missed as these facilities are lacking at KNH. Also the diagnosis of sputum negative pulmonary tuberculosis (TB) and extrapulmonary TB is difficult due to unavailability of TB culture.
- Confounders such as malnutrition, diet, genetic determination of weight and concurrent non-HIV illness may have altered the clinical presentation as well as the CD4 cell count independent of the HIV disease.

12.0 RECOMMENDATIONS

- Larger studies and community based studies need to be carried out to confirm the utility of using the WHO clinical staging alone in the absence of CD4 counts testing services in Kenya.

- There is need to provide CD4 counts testing services to all HIV patients at first contact at KNH in order to correctly identify patients with advanced immunologic disease despite mild clinical disease.

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APPENDIX 1: CONSENT EXPLANATION

My name is Dr. Syokau Ilovi. I am a postgraduate student from department of Internal Medicine. I am conducting a study on patients at KNH.

Purpose of the study

To compare WHO clinical staging and level of CD4 cells and BMI, as well as describe the opportunistic infections of HIV infected patients not on ARVs.

The study is voluntary and you can decline or withdraw from the study without any penalty.

Procedure

If you consent to be included in the study, the following shall be carried out:

1. Filling of questionnaire about socio-demographics, past and present illnesses to help in the clinical staging.
2. Physical examination as well as laboratory tests and radiological investigations to determine the clinical staging.
3. Weight and height measurements to determine BMI.
4. Drawing of 3mls of venous blood to determine CD4 count.

Risks

Mild pain when sample of blood is being drawn.

Benefits

A copy of the results shall be availed to your primary care giver in order to help in the management of your condition.

Confidentiality

Strict confidence shall be maintained at all times and the information shall be used for purposes of the study only.

If you have any questions you can contact the following:

Dr. Syokau Ilovi

P.O. Box 1976,

Nairobi.

Telephone: 0722-233157

Prof G.N Lule

Department of clinical medicine and therapeutics

University of Nairobi

P.O. Box 1976,

Nairobi.

Prof. A.O. Obel

Department of clinical medicine and therapeutics

University of Nairobi

P.O. Box 1976,

Nairobi.

Dr. H. Irimu

Kenyatta National Hospital

P.O. Box 1976,

Nairobi.

APPENDIX 2: CONSENT FORM

I.....
after reading the consent explanation form and having been explained to by Dr.
Syokau Ilovi (principal investigator), do voluntarily agree to take part in the study on
“CORRELATION OF WHO CLINICAL STAGING AND CD4 COUNTS IN ADULT HIV/AIDS
PATIENTS AT KNH”.

I am aware that I can withdraw from the study at any point without any penalties.

SIGNED.....

THUMBPRINT.....

WITNESS.....

DATE.....

APPENDIX 3: SCREENING PROFOMA

SCREENING PROFOMA

DATE:/...../.....

STUDY NUMBER:

IP/OP NUMBER:

CONTACT: P.O. Box.....

Mobile:

AGE:.....

DATE OF BIRTH:...../...../.....

DATE OF FIRST TESTING POSITIVE FOR HIV:/...../.....

DEMOGRAPHICS

GENDER: MALE FEMALE

MARITAL STATUS: SINGLE MARRIED DIVORCED

WIDOWED SEPARATED

OCCUPATION: EMPLOYED UNEMPLOYED SELF EMPLOYED

RETIRED STUDENT

LEVEL OF EDUCATION: NONE PRIMARY SECONDARY TERTIARY

PRESENTING COMPLAINTS

.....
.....
.....
.....
.....

CURRENT MEDICAL PROBLEMS

Fever	N	Y ____ days	Night sweats	N	Y ___ days
Chills	N	Y _____ days	Fatigue	N	Y ___ days
Wt loss	N	Y _____ days	Headaches	N	Y ___ days
Dizziness	N	Y _____ days	Cough	N	Y ___ days
Swollen glands	N	Y _____ days	Diarrhea	N	Y ___ days
Itchy Rash	N	Y _____ days	Throat pain	N	Y ___ days
Backache	N	Y _____ days	Skin Infection	N	Y ___ days
Vaginal discharge	N	Y _____ days	Dysuria	N	Y ___ days
Abdominal pain	N	Y _____ days	Vulva itch	N	Y ___ days
Chest pain	N	Y _____ days	Joints pain	N	Y ___ days
Painful rash	N	Y _____ days	Abscess (es)	N	Y ___ days

PREVIOUS ILLNESSES IN THE LAST TWO YEARS

Pulmonary Tuberculosis	N	Y	Herpes Zoster	N	Y
Bacterial Pneumonia	N	Y	Herpes Simplex	N	Y

CONCURRENT ILLNESS

.....
.....

MEDICATIONS.....

.....
.....

PHYSICAL EXAMINATION

TEMP..... °C PR...../MIN RR...../MIN BP.....mmHg

WEIGHT.....(Kg) HEIGHT.....(m) BMI.....kg/m²

LYMPH NODES

.....
SKIN AND NAILS.....

.....
MOUTH.....

.....
ENT.....

.....
EYES/ FUNDOSCOPY.....

.....
CNS.....

.....
LUNGS.....

.....
CARDIOVASCULAR SYSTEM.....

.....
GASTROINTESTINAL SYSTEM.....

.....
GENITOURINARY SYSTEM.....

.....
MUSCULOSKETAL SYSTEM.....

LABORATORY MEASURES

CD 4 CELL COUNT:.....cells/ μ l

Hb.....g/dl WBC.....x 10^9 /l platelets..... x 10^6 /l

OTHER INVESTIGATIONS (SPECIFY)- e.g LFTs, U/E/C, BLOOD CULTURE, STOOL
MICROSCOPY/MODIFIED ZN /CULTURE, URINE CULTURE, SPUTUM ZN /CULTURE, CHEST
RADIOGRAPH, CT SCAN BRAIN, MRI BRAIN, CYTOLOGY, HISTOLOGY

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CLINICAL DIAGNOSIS

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WHO CLINICAL STAGING:

APPENDIX 4: PARTEC CYTOFLOW METHOD

1. Blood is collected in EDTA (Anticoagulant) bottle and delivered to the laboratory within 5 hours.
2. 20 µl of whole blood added to the Partec test tube- a special bottle for this method.
3. Monoclonal antibodies for both CD4 and CD8 added to the whole blood in the tube.
4. Gentle mixing and incubation for 15 minutes at room temperature and protected from light.
5. Two buffers added, one to stop the reaction and the other to haemolyse red cells.
6. Analysis done within 10 minutes of adding the second buffer using the Partec Cytosflow device.

APPENDIX 5

REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS

PRIMARY HIV INFECTION

Asymptomatic

Acute retroviral syndrome

CLINICAL STAGE 1

Asymptomatic

Persistent generalized lymphadenopathy (PGL)

CLINICAL STAGE 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections of fingers

CLINICAL STAGE 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month

- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

- Unexplained anaemia (< 8 g/dl), and or neutropenia (<500/mm³) and or thrombocytopenia (<50 000/ mm³) for more than one month

CLINICAL STAGE 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection

- Progressive multifocal leukoencephalopathy (PML)
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

APPENDIX 5

WHO CLINICAL STAGING FOR ADULTS AND ADOLESCENTS: PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV/AIDS-RELATED CLINICAL EVENTS

(For use in adults and adolescents aged 15 years and above with laboratory evidence of HIV infection.)

Clinical event	Presumptive diagnosis	Definitive diagnosis
Primary HIV infection		
Asymptomatic		Detectable core P24 antigen and high blood HIV RNA, profound temporary lymphopenia and other transient blood abnormalities may occur. Not usually HIV antibody-positive until after symptoms. Seroconversion from HIV Ab-negative to Ab-positive.
Acute retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin manifestations.	
Clinical Stage 1		
Asymptomatic	No symptoms reported and no signs on examination.	Not required.
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm, in two or more non-contiguous sites, excluding inguinal nodes, in absence of known cause.	Not required but can be confirmed by histology (germinal centre hyperplasia, lymph node structure preserved).
Clinical Stage 2		
Moderate unexplained weight loss (<10% of presumed or measured body weight)	Reported weight loss but no obvious thinning of face or body.	Confirmed by documented weight loss.
Recurrent presumed bacterial RTI (two or more in any six-month period)	Symptom complex, e.g. unilateral face pain with nasal discharge (sinusitis) or painful swollen eardrum (otitis media), cough with purulent sputum (bronchitis), sore throat (pharyngitis). Two or more documented occurrences of antibiotic-responsive URTI.	Not required but may be confirmed by laboratory studies where available, e.g. culture of suitable body fluid.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Herpes zoster	Painful rash of small fluid-filled blisters in distribution of a nerve supply, can be haemorrhagic on erythematous background, and does not cross midline. Current or in the last two years. Severe or frequently recurrent herpes zoster is usually associated with more advanced HIV disease.	Not required.
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responds to antifungal treatment but may recur. Also common in nutritional deficiency, e.g. of B vitamins.	Not required.
Recurrent oral ulcerations occurring twice or more in six months	Aphthous ulceration, typically with a halo of inflammation and a yellow-grey pseudomembrane.	Not required.
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected adults. Note: scabies and obvious insect bites should be excluded.	Not required.
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting scalp, face, upper trunk and perineum. Also common in uninfected adults.	Not required.
Fungal nail infections of fingers	Fungal paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails. Also common in uninfected adults. Proximal white subungual onychomycosis is uncommon without immunodeficiency.	Not required but confirmed by culture of nail scrapings.

Clinical Stage 3		
Clinical event	Presumptive diagnosis	Definitive diagnosis
Severe unexplained weight loss (more than 10% of presumed or measured body weight)	Reported weight loss without trying, and noticeable thinning of face, waist and extremities.	Documented loss of more than 10% of body weight.
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month.	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens on microscopy and culture and no faecal leukocytes.
Unexplained persistent fever (intermittent or constant and for longer than one month)	Reports of fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Not required but confirmed if documented fever $>37.5^{\circ}\text{C}$ with negative blood culture, negative Ziehl-Nielsen (ZN) stain, negative malaria slide, normal or unchanged chest X-ray (CXR) and no other obvious foci of disease.
Oral candidiasis	Persistent creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form), not responding to local antifungal treatment.	Not required.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of the tongue, generally bilaterally, which do not scrape off.	Not required.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Pulmonary TB (current or in last two years)	Chronic (symptoms lasting three or more weeks) productive cough, haemoptysis, shortness of breath, weight loss, fever, night sweats and fatigue, no resolution of symptoms with standard broad-spectrum antibiotics, positive ZN stain. Response to standard anti-TB treatment in one month. Note: TB diagnosis and treatment should follow national or international guidelines. CD4 should be used where possible to guide therapy; very low CD4 may require urgent ART.	Not required but confirmed by positive sputum culture.
Severe presumed bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia)	Fever accompanied by specific symptoms or signs that localize infection, and response to antibiotic.	Not required but confirmed by bacteria isolated from appropriate clinical specimens.
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Not required.
Unexplained anaemia (<8g/dl), neutropenia (<1000/mm ³) or thrombocytopenia (<50000/mm ³) for more than one month	No presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO guidelines or other relevant guidelines.

Clinical event	Presumptive diagnosis	Definitive diagnosis
HIV wasting syndrome	Unexplained weight loss greater than 10% of body weight and visible thinning of face, waist and extremities; plus either unexplained chronic diarrhoea (lasting more than one month) or unexplained prolonged or intermittent fever for one month or more.	Confirmed by documented weight loss without trying; plus documented unformed stools negative for pathogens; negative for modified ZN; or Documented temperature of 37.5 °C or more on occasions with no obvious foci of disease, negative blood culture, negative malaria slide and normal or unchanged CXR.
Pneumocystis pneumonia	Dry cough, progressive shortness of breath, especially on exertion, with cyanosis, tachypnoea and fever, response to high-dose co-trimoxazole +/- prednisolone. Bilateral crepitations on auscultation with or without reduced air entry. CXR may show typical bilateral interstitial infiltrate with bat wing appearance.	Not required but confirmed by: microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent severe or radiological bacterial pneumonia (two or more episodes within one year)	Two episodes of fever, wet cough, fast and difficult breathing and chest pain. Consolidation on clinical examination and CXR. Response to antibiotics.	Not required but confirmed by culture or antigen test from appropriate specimen.
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal of more than one month, or visceral of any duration)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by recurrent HSV infection reported for more than one month. History of previous episodes. Scarring from previous episodes may be evident.	Not required for mucocutaneous HSV but required for visceral HSV. Suggestive symptoms of organ damage, e.g. bronchitis, pneumonitis, oesophagitis, colitis, encephalitis, supported by histology or culture.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Oesophageal candidiasis	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) +/- oral <i>Candida</i> . Responds to antifungal treatment.	Not required but confirmed by macroscopic appearance at endoscopy or bronchoscopy, microscopy or histology.
Extrapulmonary/disseminated TB	Systemic illness usually with prolonged fever, night sweats, weakness and weight loss. Clinical features of organs involved, e.g. focal lymphadenopathy, cold abscess, sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, lupus vulgaris. CXR may reveal diffuse uniformly distributed small miliary shadows Response to standard anti-TB treatment in one month.	Not required but confirmed by acid-fast bacilli (AFBs) seen in microscopy of cerebrospinal fluid (CSF), effusion, lymph node aspirate, urine, etc. Mycobacteria TB isolated from blood culture or any appropriate specimen except sputum or BAL. Histology (e.g. pleural or pericardial biopsy). CXR may show interstitial infiltrates. Lymphocytic CSF with typical abnormalities, no bacterial growth and negative cryptococcal antigen (CRAG).
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules. Can be confused clinically with bacillary angiomatosis, non-Hodgkin lymphoma and cutaneous fungal or bacterial infections.	Not required but may be confirmed by : <ul style="list-style-type: none"> • typical red-purple lesions seen on bronchoscopy or endoscopy; • dense masses in lymph nodes, viscera or lungs by palpation or radiology; • histology.

Clinical event	Presumptive diagnosis	Definitive diagnosis
CMV (retinitis or CMV infection of an organ other than liver, spleen or lymph nodes)	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians. Progressive floaters in field of vision, light flashes and scotoma. Typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Symptoms and signs of other organ involvement, e.g. pneumonitis, pancreatitis, colitis, cholecystitis, not responding to co-trimoxazole or antibiotics. Histology. CSF polymerase chain reaction (PCR).
CNS toxoplasmosis	Fever, headache, focal neurological signs, convulsions. Rapid response (within 10 days) to high-dose co-trimoxazole, or pyrimethamine and sulphadiazine or dindamycin.	Not required but confirmed by computed tomography (CT) scan showing single/multiple lesions with mass effect/ enhancing with contrast. If lumbar puncture (LP) performed, CSF nonspecific or normal. Resolution of findings after treatment if patient survives.
Cryptococcal meningitis or other extrapulmonary <i>Cryptococcus</i> infection	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes. Responds to antifungal therapy.	Confirmed by CSF microscopy (India ink or Gram stain). Serum or CSF CRAG-positive or culture-positive.
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings. LP should be conducted to exclude other infectious causes.	Recommended to confirm clinical features and exclude other causes including neurosyphilis: <ul style="list-style-type: none"> • brain scan by means of CT or magnetic resonance imaging (MRI) with • LP.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Disseminated non-tuberculous mycobacteria infection	No presumptive diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea. Severe anaemia and/or elevated alkaline phosphatase and/or (in case of diarrhoea) persisting AFB in the stool in spite of TB therapy. Plus: Culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
PML	No presumptive diagnosis.	Progressive focal neurological signs without headache or fever, cortical blindness, cerebellar signs, dementia. Confirmed by consistent MRI or CT scan, and biopsy. Viral PCR for Jacob Creutzfeldt virus.
Candidiasis of trachea, bronchi, lungs	No presumptive diagnosis.	Confirmed by symptoms, clinical signs suggestive of organ involvement and/or macroscopic appearance at bronchoscopy. Histology or cytology, or microscopy of specimen from tissue.
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive diagnosis.	Chronic diarrhoea, often profuse and watery, with weight loss, ± abdominal pain, nausea, vomiting; confirmed by modified ZN microscopic examination of stool. Stools observed to be unformed with organism visualized in stool sample.
Isosporiasis	No presumptive diagnosis.	Watery diarrhoea, cramps and weight loss. Symptoms usually indistinguishable from those of cryptosporidiosis. Isosporiasis responds to high-dose cotrimoxazole.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Any disseminated mycosis (e.g. coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Clinical symptoms nonspecific, e.g. skin rash, cough, shortness of breath, fever, anaemia, weight loss. CXR: infiltrates or nodules. Confirmed by direct microscopy. Histology: usually granuloma formation. Isolation: antigen detection from affected tissue. Skin lesion culture or microscopy positive.
Recurrent non-typhoidal salmonella septicaemia (two or more episodes in last year)	No presumptive diagnosis.	Nonspecific symptoms: fever, sweats, headaches, weight loss, diarrhoea and anorexia. Confirmed by blood culture.
Lymphoma (cerebral or B cell non-Hodgkin)	No presumptive diagnosis.	Symptoms consistent with lymphoma: lymphadenopathy, splenomegaly, pancytopenia, testicular or lung mass lesions; no response clinically to antitoxoplasma or anti-TB treatment. CNS imaging: at least one lesion with mass effect on brain scan; histology.
Invasive cervical carcinoma	No presumptive diagnosis.	Persistent vaginal discharge, postcoital or intermenstrual bleeding unresponsive to appropriate antibacterial or antifungal treatment; cervical lesions visualized. Histology. Cytology, but not carcinoma in situ.
Visceral leishmaniasis	No presumptive diagnosis.	Suggestive symptoms: malaise, chronic fever, hepatosplenomegaly, pancytopenia . Amastigotes visualized or cultured from any appropriate clinical specimen.

Clinical event	Clinical diagnosis	Definitive diagnosis
HIV-associated nephropathy	No presumptive clinical diagnosis.	Further information and evidence relating to this condition and its definition are being sought. Symptoms and signs suggestive of renal disease, with no other obvious cause identified. Early morning urine protein/creatinine ratio of >200mg/mmol in absence of a urinary tract infection and absence of an axillary temperature of 38.0 °C. Renal biopsy and histology.
HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Further information and evidence relating to this condition and its definition are being sought. Exclusion of other causes of congestive cardiac failure. The left ventricle and right ventricle are enlarged. The end-diastolic and end-systolic dimensions of the left or right ventricle are increased (2 SDs from the mean for body surface area), with a reduced fractional shortening and ejection fraction (2 SDs from the mean). Echocardiography check.

APPENDIX 7

CDC CLASSIFICATION FOR HIV-INFECTED ADULTS AND ADOLESCENTS (1993)

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B Symptomatic Conditions,##* not A or C	C AIDS-Indicator Conditions*
(1) ≥ 500 cells/ μ L	A1	B1	C1
(2) 200-499 cells/ μ L	A2	B2	C2
(3) < 200 cells/ μ L	A3	B3	C3

For symptomatic conditions, see Table 1.

* For AIDS-indicator conditions, see Table 2.

•

Table 1. CDC Classification System: Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria:

- a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.
- b) They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Hairy leukoplakia, oral
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever ($>38.5^{\circ}\text{C}$) or diarrhea lasting >1 month
- Peripheral neuropathy
- Herpes zoster (shingles), involving ≥ 2 episodes or ≥ 1 dermatome

Table 2. CDC Classification System: Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 -month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 -month duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 -month duration)

- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *M kansasii* , disseminated or extrapulmonary
- *Mycobacterium tuberculosis* , pulmonary or extrapulmonary
- *Mycobacterium* , other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month

World Health Organization
GenevaOrganisation mondiale de la Santé
Genève

WEEKLY EPIDEMIOLOGICAL RECORD

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20 July 1990

65th YEAR - 65^e ANNÉE

20 juillet 1990

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Interim proposal for a WHO Staging System for HIV Infection and Disease

The present interim proposal for a WHO Staging System for HIV Infection and Disease is made with a request for comments and suggestions for possible modifications, before it is formally proposed to the scientific and medical communities. The WHO Global Programme on AIDS is particularly interested in comments on regional pathologies which could be considered as possible candidates for inclusion in the clinical axis. Likewise, comments would be appreciated on the prognostic value of the clinical conditions presented in Table 1. Comments should be addressed to: Chief, Biomedical Research Unit, Global Programme on AIDS, World Health Organization, 1211 Geneva 27, Switzerland.

The term AIDS (Acquired Immunodeficiency Syndrome) refers to the most severe clinical manifestations of infection with the human immunodeficiency virus (HIV). It includes a number of specific opportunistic infections (i.e., *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis, cytomegalovirus disease, oesophageal candidiasis), HIV-induced pathological conditions (i.e., HIV encephalopathy), and/or associated cancers (i.e., Kaposi's sarcoma). While infection is believed to persist for life in all HIV-infected individuals, few people progress to AIDS within the first 3 years of infection and by 10 years, approximately 50% of all HIV-infected persons will have developed AIDS. This progression to AIDS reflects the chronic nature of the disease, which is hallmarked by a gradual deterioration of the host's immune system. The latter is best characterized by the depletion of the CD4+ helper/inducer T lymphocytes, a key element of the immune system, the loss of which can explain most of the pathological consequences of HIV infection.

Soon after a person becomes infected, the number of CD4+ lymphocytes begins to drop from its normal value of about 1 000 cells per mm³, at a variable rate of approximately 40 to 80 cells per mm³ per year. This progressive deterioration of the immune system is initially manifested by less severe clinical conditions, including generalized lymphadenopathy, diarrhoea, weight loss, oral candidiasis, etc. Usually, most AIDS-defining conditions occur in patients with less than 200 CD4+ lymphocytes per mm³.

SYNDROME D'IMMUNODÉFICIENCE ACQUISE (SIDA)

Echelle provisoire OMS proposée pour la détermination des stades de l'infection et de la maladie à VIH

Les lecteurs sont invités à faire part de leurs remarques et à suggérer d'éventuelles modifications concernant la proposition faite ici d'échelle OMS de détermination des stades de l'infection et de la maladie à VIH, avant que cette échelle ne soit proposée officiellement à la communauté scientifique et médicale. Le programme mondial de lutte contre le SIDA de l'OMS s'intéresse tout particulièrement aux pathologies régionales dont certaines caractéristiques seraient susceptibles de figurer parmi les paramètres cliniques. De même, une discussion de la valeur pronostique des observations cliniques présentée au Tableau 1 serait intéressante. Correspondance à adresser au Chef de l'Unité Recherche biomédicale, Programme mondial de Lutte contre le SIDA, Organisation mondiale de la Santé, 1211 Genève 27 (Suisse).

Le terme de SIDA (syndrome d'immunodéficience acquise) se rapporte aux manifestations cliniques les plus sévères de l'infection par le virus de l'immunodéficience humaine (VIH). Il comprend un certain nombre d'infections opportunistes spécifiques (pneumopathie à *Pneumocystis carinii*, toxoplasmose cérébrale, cytomégalovirose, candidose oesophagienne), des pathologies induites par le VIH (encéphalopathie à VIH) et/ou des cancers associés (sarcome de Kaposi). Si l'infection est supposée être définitive chez tous les sujets contaminés par le VIH, l'évolution vers le SIDA est rare au cours des 3 premières années, et 10 ans après la contamination, la moitié environ des sujets infectés font un SIDA. Cette évolution vers le SIDA traduit la chronicité de la maladie, attestée par la détérioration progressive du système immunitaire de l'hôte. Cette dégradation se caractérise par une disparition des lymphocytes T CD4+ auxiliaires/inducteurs, éléments clés du système immunitaire, dont la raréfaction peut expliquer la plupart des manifestations pathologiques de l'infection à VIH.

Peu après la contamination, le nombre de lymphocytes CD4+, dont la numération normale est voisine de 1 000 par mm³, commence à chuter, à la vitesse variable de 40 à 80 lymphocytes par mm³ par an. Cette détérioration progressive du système immunitaire se manifeste au début par un tableau clinique pas trop sévère, où l'on trouve adénopathie généralisée, diarrhée, perte de poids, candidose buccale, etc. Ordinairement, la plupart des états pathologiques qui définissent le SIDA surviennent quand la numération des lymphocytes CD4+ est inférieure à 200 par mm³.

Epidemiological notes contained in this issue

Acquired immunodeficiency syndrome (AIDS), air-
port malaria, cholera, Reye syndrome.
List of infected areas, p. 227.

Informations épidémiologiques contenues dans ce numéro

Choléra, paludisme d'aéroport, syndrome de Reye, syn-
drome d'immunodéficience acquise (SIDA).
Liste des zones infectées, p. 227.

Table 1. Proposed Clinical Staging System for HIV Infection and Disease
Tableau 1. Classification en stades cliniques proposée pour l'infection et la maladie à VIH

<p>Clinical stage 1:</p> <ol style="list-style-type: none"> Asymptomatic. Persistent generalized lymphadenopathy (PGL). <p>Performance scale 1: asymptomatic, normal activity.</p>	<p>Stade clinique 1:</p> <ol style="list-style-type: none"> Patient asymptomatic. Adénopathie persistante généralisée <p>Degré d'activité 1: patient asymptomatique, activité normale.</p>
<p>Clinical stage 2:</p> <ol style="list-style-type: none"> Weight loss, <10% of body weight Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis). Herpes Zoster, within the last 5 years. Recurrent upper respiratory tract infections (i.e., bacterial sinusitis). <p>And/or Performance scale 2: symptomatic, normal activity.</p>	<p>Stade clinique 2:</p> <ol style="list-style-type: none"> Perte de poids, <10% du poids corporel. Manifestations cutanéomuqueuses mineures (dermatite séborrhéique, prurigo, atteinte fongique des ongles, ulcérations buccales récurrentes, chéilite angulaire). Zona, au cours des 5 dernières années. Infections récidivantes des voies respiratoires supérieures (sinusite bactérienne, par exemple). <p>Eti/ou degré d'activité 2: patient symptomatique, activité normale.</p>
<p>Clinical stage 3:</p> <ol style="list-style-type: none"> Weight loss, >10% of body weight. Unexplained chronic diarrhoea, >1 month. Unexplained prolonged fever (intermittent or constant), >1 month. Oral candidiasis (thrush). Oral hairy leukoplakia Pulmonary tuberculosis, within the past year. Severe bacterial infections (i.e., pneumonia, pyomyositis). <p>And/or Performance scale 3: bed-ridden, <50% of the day during the last month</p>	<p>Stade clinique 3:</p> <ol style="list-style-type: none"> Perte de poids, >10% du poids corporel. Diarrhée chronique inexpliquée, >1 mois. Fièvre prolongée inexpliquée (intermittente ou constante), >1 mois. Candidose buccale (muguet). Leucoplasie chevelue buccale Tuberculose pulmonaire, dans l'année précédente. Infections bactériennes sévères (pneumopathie, pyomyosite, par exemple). <p>Eti/ou degré d'activité 3: patient alité, <50% de la journée pendant le dernier mois.</p>
<p>Clinical stage 4:</p> <ol style="list-style-type: none"> HIV wasting syndrome, as defined by CDC.^a <i>Pneumocystis carinii</i> pneumonia. Toxoplasmosis of the brain. Cryptosporidiosis with diarrhoea, >1 month. Cryptococcosis, extrapulmonary. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes. Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration Progressive multifocal leukoencephalopathy (PML). Any disseminated endemic mycosis (i.e., histoplasmosis, coccidioidomycosis). Candidiasis of the oesophagus, trachea, bronchi or lungs. Atypical mycobacteriosis, disseminated. Non-typhoid <i>Salmonella</i> septicaemia. Extrapulmonary tuberculosis. Lymphoma. Kaposi's sarcoma (KS). HIV encephalopathy, as defined by CDC.^b <p>And/or Performance scale 4: bed-ridden, >50% of the day during the last month.</p> <p>(Note: Both definitive and presumptive diagnoses are acceptable.)</p>	<p>Stade clinique 4:</p> <ol style="list-style-type: none"> Syndrôme cachectique du VIH, selon la définition des CDC.^a Pneumopathie à <i>Pneumocystis carinii</i>. Toxoplasmose cérébrale. Cryptosporidiose accompagnée de diarrhée, >1 mois. Cryptococcose, extrapulmonaire. Cytomégalovirose (CMV) touchant un autre organe que le foie, la rate ou les ganglions lymphatiques. Herpès (HSV), cutanéomuqueux >1 mois, ou viscéral quelle que soit sa durée. Leucoencéphalopathie multifocale progressive. Toute mycose endémique généralisée (histoplasmosse, coccidioidomycose, par exemple). Candidose de l'oesophage, de la trachée, des bronches ou des poumons. Mycobactériose atypique, généralisée. Septicémie à salmonelles non typhiques. Tuberculose extrapulmonaire. Lymphome. Sarcome de Kaposi (SK). Encéphalopathie à VIH, selon la définition des CDC.^b <p>Eti/ou degré d'activité 4: patient alité, >50% de la journée pendant le dernier mois.</p> <p>(Remarque: Les diagnostics sont acceptables, qu'ils soient de certitude ou présumés.)</p>

^a 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)

^b 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 that could explain the findings

(See No 1/2, 1988, p 6.)

^a Syndrôme cachectique du VIH: Perte de poids >10% du poids du corps, plus diarrhée chronique inexpliquée (>1 mois), ou anémie chronique accompagnée de fièvre prolongée inexpliquée (>1 mois).

^b Encéphalopathie à VIH: Manifestations cliniques consistant en dysfonctionnement cognitif et/ou moteur empêchant, perturbant les activités quotidiennes, évoluant depuis plusieurs semaines à plusieurs mois, en l'absence d'affection ou de maladie concomitante non due au VIH et susceptible d'expliquer le tableau clinique.

(Voir N° 1/2, 1988, p 6.)

From the asymptomatic stage to the stage when AIDS-defining conditions occur, the natural history of HIV infection is characterized by increasingly severe clinical manifestations and immunological alterations, which indicate the gradual deterioration of the immune system induced by the virus. All these changes have been used, to a variable extent, as predictors of disease progression and, in some instances, as component milestones of "staging systems" for HIV infection.

Entre le stade asymptomatique et la survenue des pathologies définissant le SIDA, l'histoire naturelle de l'infection à VIH est caractérisée par des manifestations cliniques et des altérations immunologiques de plus en plus graves qui signalent l'amputation progressive du système immunitaire induite par le virus. Toutes ces altérations ont plus ou moins été utilisées comme éléments prédictifs de l'évolution de la maladie, et dans certains cas comme repères constitutifs d'une détermination des stades de l'infection à VIH.

With the pandemic spread of AIDS, a universally applicable staging system for HIV infection and disease is needed. This system could be used to: improve clinical management of patients; establish reliable prognoses; help in designing and evaluating drug and vaccine trials; and perform studies on pathogenesis and natural history of HIV infection.

However, the staging systems developed so far (such as the Walter Reed System) do not meet the criteria of worldwide applicability, as their component laboratory markers are unavailable in many areas of the world. Additionally, the clinical experience accumulated over the last few years may now permit the assignment of a more definitive prognostic significance to a larger number of HIV-related clinical features, whose predictive value was still unknown at the time those systems were proposed.

On the other hand, classification systems of HIV infection (like the Centers for Disease Control [CDC] classification) are mainly descriptive in nature and therefore do not fulfil the criterion of predictivity that is essential for a staging system.

The Global Programme on AIDS of the World Health Organization addressed these issues during a consultation on "Staging Criteria of HIV Infection" which was convened in Geneva on 24-26 July 1989. As a result of that consultation, a draft proposal for clinical staging of HIV infection was developed and a preliminary validation exercise was conducted to assess the feasibility of the proposed system.

Since the use of survival time as a validation criterion would have required a long prospective study, it was decided to first conduct a worldwide cross-sectional study, where clinical conditions were correlated with laboratory markers already known to reflect disease progression (particularly CD4 numbers), using the latter as surrogates of survival. This validation exercise involved data on 907 HIV-antibody positive patients collected in 26 clinical centres from each of the 5 continents. The results of this validation exercise were reviewed by a Technical Working Group that met in Geneva on 21-23 February 1990, and which developed the present proposal.

A list of clinical markers which were felt to have prognostic significance was assembled, encompassing the simplest to the most complex level of diagnostic accuracy (from signs and symptoms only to identification of the etiological agent). The list was hierarchically organized into the following 4 prognostic categories:

1. asymptomatic/persistent generalized lymphadenopathy (PGL);
2. early (mild) disease;
3. intermediate (moderate) disease; and
4. late (severe) disease (basically equivalent to AIDS).

In addition to placement in a category based on clinical conditions, the following performance scale (a modification of the Eastern Cooperative Oncology Group score) was incorporated into the system:

1. asymptomatic, normal activity;
2. symptomatic, normal activity;
3. bed-ridden, <50% of the day; and
4. bed-ridden, >50% of the day.

The proposed WHO Staging System for HIV Infection and Disease is primarily based on clinical criteria. Symptoms, signs and diseases should be defined according to medical judgment. Patients, who should be confirmed HIV-antibody positive and 13 years of age or older, are clinically staged (categories 1, 2, 3, 4) on the basis of the presence of the clinical condition, or performance score, belonging to the highest level (Table 1).

However, a further refinement of the system would also include, in addition to the "clinical axis", a "laboratory axis" (Fig. 1). The laboratory axis, if available, will subdivide each clinical category into 3 strata (A, B, C), depending on the number of CD4 lymphocytes per mm³ (>500, 200-500, <200). If CD4 counts are not available, total lymphocytes should be explored as an alternative laboratory marker, also in 3 different strata

Le SIDA se propageant sur le mode pandémique, une détermination des stades de l'infection et de la maladie à VIH universellement applicable s'impose. L'intérêt d'un tel système est multiple: améliorer la prise en charge clinique des patients, faire un pronostic fiable; aider à la conception et à l'évaluation des essais de médicaments et de vaccins; investiguer la pathogénie et l'histoire naturelle de l'infection à VIH.

Les échelles de détermination des stades élaborées jusqu'ici (comme celle du *Walter Reed Institute*) ne sont pas partout applicables dans la mesure où les marqueurs biologiques constitutifs sur lesquels ils s'appuient sont inutilisables dans bien des régions. Ajoutons que l'expérience clinique accumulée au long des dernières années permet maintenant de donner une valeur pronostique plus sûre à un nombre plus grand de manifestations cliniques liées au VIH, alors que leur valeur prédictive était encore inconnue au moment où les classifications précédentes avaient été proposées.

D'autre part, les classifications de l'infection à VIH (comme celle des *Centers for Disease Control* [CDC]) sont essentiellement descriptives et donc dépourvues du caractère prédictif indispensable à un système de détermination des stades.

Le programme mondial de lutte contre le SIDA de l'Organisation mondiale de la Santé s'est penché sur ces questions au cours d'une consultation sur les critères de détermination des stades de l'infection à VIH organisée à Genève du 24 au 26 juillet 1989. A la suite de cette consultation, un projet de proposition de classification en stades cliniques de l'infection à VIH a été élaboré et un premier essai de validation réalisé en vue de déterminer l'applicabilité du système proposé.

L'utilisation du temps de survie comme critère de validation aurait demandé une longue étude prospective, aussi-a-t-il été décidé de réaliser tout d'abord une étude transversale mondiale, dans laquelle les manifestations cliniques seraient corrélées aux marqueurs biologiques déjà connus pour refléter l'évolution de la maladie, en particulier le nombre de CD4, utilisant ce dernier pour remplacer la survie. Cet essai de validation a réuni les données concernant 907 séropositifs recrutés dans 26 centres cliniques des 5 continents. Les résultats de cet essai de validation ont été examinés par un groupe de travail technique qui s'est réuni à Genève du 21 au 23 février 1990 et qui a élaboré la présente proposition.

Une liste des marqueurs cliniques censés avoir une valeur pronostique a été dressée, impliquant une précision diagnostique variable, minimale pour les seuls symptômes, maximale pour l'identification de l'agent étiologique. Les marqueurs ont ensuite été répartis en 4 catégories hiérarchisées:

1. infection asymptomatique/adénopathie persistante généralisée;
2. début de maladie (maladie bénigne);
3. stade intermédiaire (maladie modérée);
4. stade avancé (maladie sévère — l'équivalent du SIDA).

A la définition de catégories s'appuyant sur la clinique, a été ajoutée une échelle de l'activité du malade (une variante du système de notation de l'*Eastern Cooperative Oncology Group*):

1. patient asymptomatique, activité normale;
2. patient symptomatique, activité normale;
3. patient alité, moins de 50% de la journée;
4. patient alité, plus de 50% de la journée.

L'échelle OMS proposée pour la détermination des stades de l'infection et de la maladie à VIH s'appuie essentiellement sur des critères cliniques. La définition des symptômes et des affections doit être conforme à la pratique médicale reconnue. Le patient, dont la séropositivité au VIH doit être confirmée et l'âge supérieur ou égal à 13 ans, est placé dans l'une des catégories cliniques (catégories 1, 2, 3, 4) selon la présence des manifestations cliniques ou son degré d'activité, le stade retenu étant le plus avancé (Tableau 1).

Une précision supplémentaire est apportée à ce système en ajoutant à l'axe «paramètres cliniques», un axe «paramètres biologiques» (Fig. 1). Chacune des catégories cliniques est subdivisée selon l'axe paramètres biologiques en 3 niveaux (A, B, C) suivant le nombre de lymphocytes CD4 par mm³ (>500, 200-500, <200). Si la numération des CD4 ne peut être réalisée, on utilisera alors comme marqueur biologique le nombre total de lymphocytes, avec de nouveau 3 niveaux

(>2 000, 1 000-2 000, <1 000). Patients would then be classified as 1A, 1B, etc. A suffix could be used to indicate if the laboratory classification is based on CD4 numbers (c) or lymphocyte counts (l) (i.e., 1Ac, 2Bl). If laboratory values are not available, patients could be classified as 1X, 2X, 3X or 4X, or simply as 1, 2, 3 or 4.

(>2 000, 1 000-2 000, <1 000). Si ces numérations sont pratiquées, le patient peut alors être rangé dans les catégories 1A, 1B, etc. Une lettre ajoutée à chacune des catégories peut indiquer si le résultat de laboratoire correspond au nombre de CD4 (c) ou au nombre de lymphocytes (l) (par exemple, 1Ac, 2Bl). En l'absence de données biologiques, le patient peut être rangé dans les catégories 1X, 2X, 3X ou 4X, ou plus simplement 1, 2, 3 ou 4.

Fig. 1

WHO Staging System for HIV Infection and Disease: clinical/laboratory classification

Echelle OMS de détermination des stades de l'infection et de la maladie à VIH: classification clinique/biologique

Laboratory axis Axe paramètres biologiques			Clinical axis Axe paramètres cliniques			
Lymphocytes	or/ou	CD4	(1) Asymptomatic/persistent generalized lymphadenopathy Patient asymptomatique/ adénopathie persistante généralisée	(2) Early Début	(3) Intermediate Intermédiaire	(4) Late Tardif
			(A)	>2 000	>500	1A
(B)	1 000-2 000	200-500	1B	2B	3B	4B
(C)	<1 000	<200	1C	2C	3C	4C

An advantage of the proposed system is that the clinical/laboratory classification can be done even in the absence of definitive information on prognostic value of all the possible combinations ("cells") and will provide a useful reference framework for comparing results of investigations done in different parts of the world, stimulating at the same time the research needed to better understand their prognostic significance. Another advantage of this system is that it does not call for "reclassification" of the patients, when additional laboratory information is obtained, or when the prognostic significance of some of the clinical/laboratory combinations is better understood.

Un des avantages du système proposé est que la classification associant critères cliniques et biologiques est réalisable même si la valeur pronostique de toutes les combinaisons possibles (les cases du tableau) n'est pas connue avec certitude et qu'elle constitue une référence utile pour comparer les résultats d'investigations effectuées dans différentes régions du monde, stimulant du même coup la recherche pour mieux définir la valeur pronostique. Le système proposé a un autre avantage: la « reclassification » des patients n'est pas nécessaire lorsqu'on obtient des données biologiques nouvelles ou que la valeur pronostique de certaines des combinaisons est mieux connue.

The relative prognostic value of staging using a combination of clinical and laboratory markers will have to be defined by longitudinal studies.

La valeur pronostique relative de la détermination des stades associant marqueurs cliniques et biologiques devra être définie au moyen d'études longitudinales.

AIRPORT MALARIA

SWITZERLAND. — Five cases of airport malaria were reported in 1989 in Geneva. Between 14 July and 2 August 1989, 5 residents, living less than 2 km from Geneva International Airport, were hospitalized and diagnosed with malaria (3 at Geneva University Hospital, 2 in Pesaro, 2 weeks after having travelled by road to Italy). None had received a blood transfusion, an intravenous (IV) injection, or had visited a tropical area, except for 1, a former pilot, whose last brief visit was a year earlier.

PALUDISME D'AÉROPORT

SUISSE. — Cinq cas de paludisme d'aéroport ont été signalés en 1989 à Genève. Entre le 14 juillet et le 2 août 1989, 5 résidents, domiciliés à moins de 2 km de l'aéroport international de Genève, ont été hospitalisés (3 à l'Hôpital universitaire de Genève, 2 à Pesaro, arrivés en voiture en Italie 2 semaines auparavant); dans chaque cas, le paludisme a été diagnostiqué. Aucun d'entre eux n'avait reçu de transfusion sanguine ou d'injection par voie intraveineuse et aucun ne s'était rendu dans un pays tropical, sauf 1, un ancien pilote, dont le bref séjour remontait à 1 an.

All patients had a fever > 40 °C, accompanied by nausea, vomiting, headache, or diarrhoea. Two of the 5 patients had some degree of mental confusion. Typhoid fever or Gram negative sepsis was suspected in 1 patient and otitis media in another. For these 2 patients, the lack of response during antibiotic therapy led to further investigations and the discovery of blood parasites. A third patient had been treated with co-trimoxazole for a suspected urinary infection, leading to defervescence, followed by a relapse of the fever 9 days later.

Tous les malades avaient une fièvre de 40 °C ou plus et souffraient de nausées, de vomissements, de maux de tête ou de diarrhée. Deux des 5 patients présentaient une certaine confusion mentale. La fièvre typhoïde ou une septicémie à germes Gram négatifs a été soupçonnée chez 1 malade et une otite moyenne chez un autre. L'antibiothérapie étant restée sans effet chez ces 2 malades, la poursuite des recherches a permis de découvrir la présence de parasites dans le sang. Un troisième malade, soupçonné d'avoir une infection urinaire, avait été traité à la cotrimoxazole; après la défervescence consécutive au traitement, la fièvre a réapparu 9 jours plus tard.

Plasmodium falciparum trophozoites were detected in all 5 patients. Three had a parasitaemia ≥ 10% and all experienced anaemia (haemoglobin: 6.9-9.8 g%) with the exception of the patient treated with cotrimoxazole. In this patient *P. falciparum* trophozoites were only detected 31 days after onset of the disease on a second recrudescence following presumptive treatment with chloroquine. It took 5 to 7 days from the beginning of the symptoms to establish a correct diagnosis for the other 4 patients. All recovered. Four required standard IV quinine treatment. The average length of hospitalization was 14.4 days.

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Des trophozoïtes de *Plasmodium falciparum* ont été découverts chez les 5 malades. Trois présentaient une parasitémie ≥ 10% et tous souffraient d'anémie (hémoglobine: 6,9-9,8 g%), à l'exception du malade traité à la cotrimoxazole. Chez ce malade, les trophozoïtes de *P. falciparum* n'ont été découverts que 31 jours après le début de la maladie lors d'une deuxième rechute suivant un traitement présumé à la chloroquine. Pour les 4 autres malades, il a fallu de 5 à 7 jours après l'apparition des premiers symptômes pour poser un diagnostic correct. Tous se sont rétablis. Le traitement type à la quinine par voie intraveineuse a été nécessaire chez 4 d'entre eux. La durée moyenne d'hospitalisation a été de 14,4 jours.