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CORRELATION OF WHO CLINICAL STAGING WITH CD4 COUNTS IN ADULT HIV / AIDS PATIENTS AT KENYATTA NATIONAL HOSPITAL, NAIROBI
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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*: One hundread and fifty two newly diagnosed HIV patients were recruited prospectively. Patients were first staged using the 2005 WHO clinical staging and then blood drawn for CD4 cell count.**
***Results*: The mean age in the study was 35 years, with females comprising 52.6% 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 >350cells/μl was 63% with a specificity of 82%. The most common 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/μl.**

INTRODUCTION

The Human Immunodeficiency Virus (HIV) infects and destroys CD4+ T lymphocyte cells, leading to their persistent decline in number and function as the disease progresses (1-7).

Since the first cases of HIV were described (8-10), various clinical staging systems have been developed after observations that different opportunistic infections occurred at specific CD4 T-cell counts. The most widely used are the Centre for Disease Control (CDC) classification and the World Health Organization (WHO) clinical staging.

The WHO clinical staging was first developed in 1990 (11), and emphasised 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 and can be used to guide HIV care even in the absence of CD4 T-cell count. This is unlike the CDC classification which requires both the clinical stage and CD4 count for classification. The WHO staging has been revised severally with the current one produced in 2005 (12).

The WHO clinical staging is a tool that was designed to identify HIV / AIDS related clinical events using clinical presentation and simple laboratory and radiological investigations, with the clinical diagnosis being either presumptive or definitive depending on the tiers of investigation carried out. This has enabled WHO as well as countries in Africa, particularly Sub-Saharan Africa, which has borne the brunt of the HIV / AIDS pandemic, to provide HIV care and treatment with limited resources.

Being a symptom based tool, the WHO clinical staging may not correctly identify the opportunistic infections. Similarly, patients may have no clinical symptoms despite low CD4 T-cell counts. Thus, if used alone, the WHO clinical stage may disqualify patients for initiation of HAART despite advanced immunologic disease.

CD4 T-cell count is the single most useful parameter for evaluation of HIV disease as well as for prognostication. Where available, it forms the cornerstone of HIV/AIDS care as manifestation of opportunistic infections correlate with the level of CD4 counts. However, it is expensive and is not readily available.

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

MATERIALS AND METHODS

A prospective study was carried out by recruiting newly diagnosed HIV positive patients aged between 18 and 49 years presenting either to the inpatient medical wards or the outpatient HIV clinic. A total of 152 patients were recruited, 76 from the outpatient clinic, 76 from the medical wards. The mean duration of diagnosis was nine days and had not been on cotrimoxazole prophylaxis prior to recruitment into the study. Patients who were on steroids, cytotoxic drugs or with a non-HIV malignancy were excluded from the study. Patients were evaluated and staged using the Interim WHO 2005 clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance (African region) (12). Laboratory and radiological methods were carried out if they were required to make a clinical diagnosis. In the majority of the cases, the HIV clinical events were presumptive diagnosis and based on the WHO clinical staging for adults and adolescents: presumptive and definitive criteria for recognising HIV/AIDS related clinical events (12).

Blood for CD4 T-cell count was drawn after the clinical staging had been done. Level of CD4 count was determined using Partec Cytoflow method, with the results made available after one to four days.

Analysis of the Data was done using SPSS 17.0. Student t-test was used for continuous variables and chi-square for proportions. Correlation was done using spearman's rank correlation coefficient. Two by two tables were used to calculate sensitivity, specificity, positive predictive value and negative predictive value.

RESULTS

The study was carried out between April 2010 and February 2011 both in the outpatient HIV clinic as well as inpatient medical wards. The patient characteristics were tabulated as shown.

Table 1
Socio-demographic profile (N=152)

Socio-demographi characteristics	All patients (N=152) No (%)
Age –years ±2SD	35.25 ±1.71
Female sex	80(52.6)
Marital status-married	100 (65.1)
Education primary and below	71 (46.7)
Education secondary and above	81 (53.3)
Occupation employed	87 (57.2%)
Mode of hiv diagnosis (VCT)	70 (46.1)
Mode of hiv diagnosis (PITC)	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 school education.

Table 2
Prevalence of HIV/AIDS related clinical events (N=152)

HIV/AIDS related 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%)
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/ AIDS related clinical events were bacterial infections (34%), severe weight loss (28%) and Tuberculosis (27%).

Table 3
Comparison of clinical staging and CD4 count difference (N=152)

WHO clinical stage	Mean	Median	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	-

There was correlation between the mean CD4 T-cell counts in comparison to the WHO guidelines recommendations in Stages 2, 3 and 4 with the mean and 95% confidence interval being within the expected values.

The mean CD4 count in Stage 1 was lower than expected from the WHO guidelines.

Spearman's correlation coefficient between the WHO clinical staging and CD4 count was -0.583 ($p < 0.01$).

Table 4
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/μl was 53% with specificity of 89%. The positive predictive value was 80% and the negative predictive value= 71%

Table 5
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/μl was 63% with specificity of 82%. The positive predictive value was 53% and the negative predictive value was 87%.

DISCUSSION

The WHO clinical staging was 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 1990 (11) after observations that certain opportunistic infections occurred at specific CD4 T-cell counts. Our study was carried out using the interim WHO 2005 clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance (African region) (12).

In this study, 152 newly diagnosed HIV patients diagnosed either by rapid test or Elisa method were recruited. Diagnosis was either through the outpatient voluntary counselling and testing (VCT) or through provider initiated testing and counselling (PITC). The mean duration of HIV diagnosis at recruitment was nine days. Patients recruited into the study were HAART-naive and had never used cotrimoxazole prophylaxis.

The overall sex distribution was 52.6% female and 47.4% male. Outpatient arm comprised of 53.9% female and 46.1% male. Inpatient arm was 51.3% female and 48.7% male. Studies carried out in the comprehensive care centre (CCC) have shown a higher female preponderance (13-15).

The Kenya 2009 Population and Housing Census showed that an almost equal male to female ratio countrywide as well as in Nairobi province (16). HIV prevalence studies done in Kenya have shown both higher rates of HIV as well as higher HIV testing amongst females (17-19).

Sixty five point eight percent of the patients were married. This concurs with other studies that have shown almost half of new HIV infections occur among married couples (18,20).

The most common HIV/AIDS related clinical events in this study was bacterial infection which occurred in 51 patients (34%). Tuberculosis (both pulmonary and extrapulmonary) was the third most common and was diagnosed in 41 patients (27%). Cryptococcal meningitis was diagnosed in eight of our patients (5%). Most of these were presumptive clinical diagnosis as histopathologic diagnosis was lacking. The high incidence in TB in the study population is in keeping with the national estimates. According to National/AIDS/STD Control Program (NASCOP) and the National Tuberculosis and Leprosy Program, TB is the most common opportunistic infection in persons living with HIV/AIDS and accounts for a third of all AIDS related deaths.

In patients who had chest radiographs done as part of the workup for the illness, 22 had a radiologic diagnosis of TB (55%) while three patients had features of pneumonia (7.5%). Thirteen patients had chest radiographs reported as normal despite having symptoms of respiratory disease. Two patients had no radiological evidence of pulmonary TB despite having sputum positive for AAFBs.

In this 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. Most of the patients in our series presented with severe symptomatic disease despite the availability of free VCT services countrywide. According to the National AIDS/STD Control Program (NASCOP), there are 156 registered VCTs in Nairobi and 952 countrywide (21). The KAIS 2007 (18) 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 either through VCT or PITC services only after they have symptomatic and advance disease.

Similarly, 75% of the patients in this series presented with CD4 T-cell counts of <350 cells/μl.

Overall, more than 70% of our patients qualified for HAART at the very onset based on their CD4 cell count or clinical stage and were in urgent need for commencement of HAART.

Our study found an overall mean CD4 T-cell count of 455 for Stage 1, 420 for Stage 2, 203 for Stage 3 and 92 for Stage 4. The mean CD4 T cell counts in all the 4 clinical stages were less than 500 cells/μl. These results are comparable to other studies carried out by Edathoju *et al* in Saudi Arabia (22) and Kassa *et al* in Addis Ababa (23) which demonstrated correlation with CD4 T-cell counts. These findings support the use of WHO clinical staging as a surrogate marker for the level of immunosuppression in leau of CD4 T-cell counts.

Using the previous WHO cutoff for initiation of HAART of 200 cells/μl, our study had a sensitivity of 53% and specificity of 89%. Similar results were reported in other studies (24-27). Kaagayi *et al* (25) found a sensitivity 51% and specificity of 88% with CD4 cutoffs of 200 cells/μl. In a study by Jaffar *et al* (25) sensitivity was 52% and specificity 68% of the clinical staging to predict CD4 counts of 200cells/μl. In a study carried out in Thailand by Costello *et al* (26) the WHO clinical staging criteria had a sensitivity of 33% in identifying patients with CD4 counts of 200cells/μl. A similar study carried out in Tanzania by Morpeth *et al* (27) 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/μl is used.

In this study, the WHO clinical stage had a sensitivity of 63% in correctly predicting CD4 counts greater than 350 cells/μl and specificity of 82% in identifying patients with CD4 counts less than 350 cells/μl. A similar study carried out at Makerere University in Kampala by Baveewo *et al* (28) found that in WHO Clinical Stage 1 and 2, the sensitivity to predict CD4 T-cell counts of 350 cells/μl 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/μl qualify for initiation of HAART.

In this study 21 (14%) of the patients with clinical stage 1 and 2 had CD4 counts below 200 cells/μl; of these, 12 (8%) had CD4 counts between 200 and 350 cells/μl, while 9 (6%) had CD4 counts below 200 cells/μl. 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/μl as compared to the 12 patients with CD4 counts between 200 and 350 cells/μl. Wilkin *et al* (29) demonstrated that the optimal time for initiation of HAART was when CD4 T-cell counts fell to below 350 cells/μl in order to prevent both HIV-related as well as non-HIV-related clinical events. A similar study carried out by Kaplan *et al* (30) 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/μl (Hazard ratio 3.5) as compared to CD 4 counts of 200- 350 cells/μl (Hazard ratio 1.7) in comparison to patients with CD4 counts of greater than 500 cells/μl.

By increasing the cutoff for HAART from 200 cells/μl to 350 cells/μl, the sensitivity of the study increased from 53% to 63% with a slight decline of specificity from 89% to 82%. Thus, the WHO clinical staging has became a more relevant tool in identifying patients in need of HAART with the use of the current guidelines of 350 cells/μl as compared to the previous guidelines of 200 cells/μl. 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/μl. However, the sensitivity was low and missed 37% of patients with CD4 T-cell count of less than 350 cells/μl. These results are comparable to studies done elsewhere which demonstrate the low sensitivity of the WHO clinical staging (25-28).

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