Efficacy of total lymphocyte count as a surrogate for CD4 cell counts in HIV-infected adults in the era of higher treatment cutoffs and less funding: a cross-sectional study

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Abstract

Background: Total Lymphocyte Count (TLC) has been previously found to be a suitable surrogate for CD4 counts in the management of HIV in resource limited settings. With the new treatment cutoff of 500 cells/mm^3, its performance needs to be further evaluated.

Objective: To determine the efficacy of TLC as a surrogate for CD4 counts in a resource-limited African setting.

Methods: A retrospective, cross-sectional study was carried out using the medical database at the comprehensive care clinic for HIV patients in Consolata Hospital Nkubu, Meru county, Kenya.

Results: Of the 234 patients included in the study, 72.2% were females while 27.8% were males. 69.2% had a CD4 of 500 cells/mm^3 or less. The mean age was 35.8 years (34.0-37.6). The median CD4 count was 427 cells/mm^3 (Interquartile range-IQR, 261-676) while that of TLC was 1900 cells/mm^3 (IQR, 1400-2500). Correlations between CD4 count and TLC (r=0.582, p<0.0001) and CD4 count and age (r=-0.344, p<0.0001) were significant while that between CD4 count and haemoglobin level (0.046, p=0.484) was not. TLC cutoff of 2000 cells/mm^3 was found to best predict CD4 500 cells/mm^3 or less with a sensitivity of 78.1%, specificity of 35.9% and Positive Predictive Value (PPV) of 66.1%.

Conclusion: TLC still retains some usefulness in detecting CD4 counts of less than 500 cells/mm^3, though not as strongly as it performs with lower cutoffs.

Key words: CD4, Total lymphocyte count, Surrogate, Resource-limited settings

Introduction

HIV/AIDS continues to be a major disease burden particularly in resource limited settings, and more specifically, in sub-Saharan Africa. In the last few years, two major events that will have a lasting impact in sustaining the gains in control of the pandemic have taken place. First, the US government decided that it had reached a turning point in its emergency response to HIV/AIDS and announced a gradual reduction of its funding to many of the countries benefitting from the President's Emergency Plan for Aids Relief (PEPFAR) with final aim of transferring the care of patients back to clinics run by the respective governments [1].

Second, in June 2013, the WHO released new guidelines for the management of HIV which raised the minimum cut-off for initiation of Highly Active Antiretroviral Therapy (HAART) from 350 to 500 cells per mm^3 [2]. This is an unfortunate paradox as more patients will be enrolled for HAART when the donor funds supporting the initiative in Africa continue to dry up. Most of the benefitting countries may lack both financial and human resource capabilities to effectively manage the transition, as it has already become apparent in South Africa [3]. In Kenya, the lowest level of the healthcare system that can effectively handle these patients is the health centers, owing to their countrywide distribution [4]. However this level of the Kenyan healthcare system may not have both the personnel and equipments needed in managing HIV patients in the complexity of provision of HAART and both screening

and treating opportunistic infections [5]. This includes physicians and equipments for checking CD4 counts and viral load determinations. Therefore there is need for concerted efforts from all stakeholders to develop cost-effective, sustainable, accessible and feasible health systems to support these patients to avoid discontinuation of care. Total Lymphocyte Count (TLC) has long been considered as a suitable surrogate marker for CD4 counts when the latter is not available, especially in resource limited settings [6-8]. However, the same has not been demonstrated in the new WHO cutoffs and with the urgency of transition from donor funded to government funded care programmes.

Our study was aimed at evaluating the TLC cut-off that would best approximate a CD4 level of 500/mm^3, as well as checking the relationship between age, haemoglobin level and CD4 counts. Unlike CD4 cell count determinations, TLC is easier to perform, requires cheaper equipment and expertise and is part of a total blood count screen that can provide additional valuable information. However it is less precise in determining the actual degree of immune suppression in HIV infected patients.

Materials and Methods

Study setting and participants: The study was carried using the electronic database of patients enrolled for care at the comprehensive care center of Consolata Hospital Nkubu, a faith-based, regional referral hospital in Meru County, Kenya. For a medical record to be included, the patient had to be above 18 years of age, enrolled into care between 2005 and 2014, and both a CD4 cell count and a full blood count had been performed at least once and entered into the database on the same visit. In cases of multiple laboratory records, the latest one was used for the study. The criteria of exclusion/inclusion was: Records of patients below 18 years of age, those with missing demographic data of age and sex, evidence of opportunistic infection in the preceding three months, as well as entries of CD4 cell counts and full blood counts performed and entered on different dates. Ethical approval for the study was granted by the institutional Ethics and Research Committee (ERC/MIN 4/2015). No consent from the patient was necessary since there was no interaction between patients and the research team.

Data analysis: Categorical variables were described using percentages while continuous variables were described using mean, median and interquartile ranges (IQR). Statistical Package for Social Sciences (SPSS version 17, Chicago, IL, USA) was used to analyze the data. Both linear and logistic regressions were used to determine whether TLC was a predictor of CD4 count in the study population. Pearson correlation coefficient was determined for age, haemoglobin level and TLC against CD4 count.

Results

A total of 234 patients were included, among which 72.2% were females while 65(27.8%) were males, mean age was 35.8 years (34.0-37.6)^3. Overall 69.2% of the patients demonstrated CD4 counts of 500 cells/mm^3 and less. The median CD4 count was 427 cells/mm (IQR; 261-676), median TLC was 1900 cells/mm^3 (IQR; 1400-2500), while the median haemoglobin level was 13.1 g/dl (IQR; 12.1-14.3), (Table 1). Correlation coefficient r between CD4 count and TLC (r=0.582, p<0.0001), (Figure 1) as well as CD4 count and age (r=-0.344, p<0.0001) was found to be significant while the correlation between CD4 count and haemoglobin level (r=0.046, p=0.484) was not statistically significant (Table 2).

Table 1: Median and interquartile ranges for CD4 count, TLC and Hb

Variable	Median	IQR
CD4 count(cells/mm^3)	427	261,676
TLC(cells/mm^3)	1900	1400,2500
Hb (g/dl)	13.1	12.1,14.3

Table 2: Correlation coefficients(r) between the TLC, Age, Hb) and CD4 count

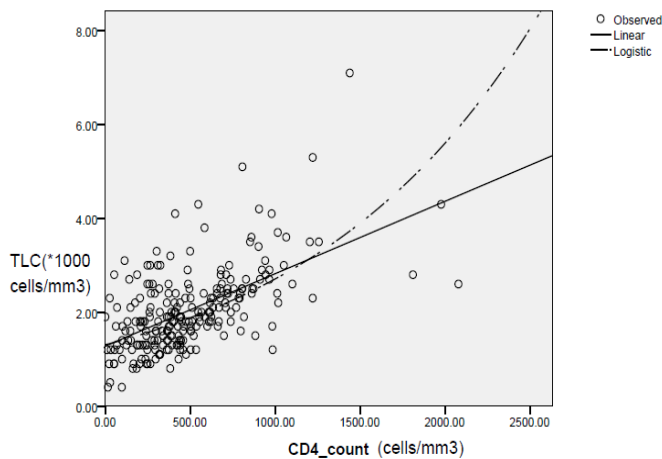| Variable	r	P-value
TLC	0.582	<0.001
Age	-0.344	<0.001
Hb	0.046	0.484

Figure 1: Scatter plot depicting the positive correlation between TLC and CD4 count.

Table 3 is the sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for TLC cutoffs of 1500, 2000 and 2500 cells/mm³ in predicting CD4 count of less than 500 cells/mm³.

For a TLC cutoff of 1500 cells/mm³, the sensitivity and NPV are high (91.4% and 75.8% respectively), while the specificity and PPV are both relatively low at approximately 40%. When the cutoff is raised to 2000 cells/mm³, the sensitivity falls to 78% while the PPV rises to 66%. For detection of a CD4 level of less than 200 cells/mm³, a cutoff of 1000 cells/mm³ has a high NPV (95.5%) while that of 1500 has specificity, PPV and NPV of 91.5, 61.1 and 75.8 % respectively (Table 4).

Table 3: Sensitivity, specificity, PPV and NPV for various TLC cutoffs to detect CD4 count of 500 cells/mm³ or less

TLC cutoff (cells/mm³)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1500	91.4	40.2	39.5	75.8
2000	78.1	35.9	66.1	58.3
2500	67.9	26.0	77.2	18.1

Table 4: Sensitivity, specificity, PPV and NPV for various TLC cutoffs to detect CD4 counts of 200 cells/mm³ or less

TLC cutoff (cells/mm³)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1000	52.6	12.1	27.8	95.5
1500	31.4	91.5	61.1	75.8

Discussion

Several studies conducted elsewhere reported that TLC is a suitable surrogate marker for CD4 counts in HIV patients [7, 9-12], though not with higher HAART initiation cutoffs of 500 cells/mm³. This is important since TLC as part of full blood count tests is widely available at an affordable cost in many African settings. It also requires relatively less expertise in performance and interpretation as compared to CD4 count or viral load determinations especially on a large scale. Although this was also the case in our study, the sensitivity, specificity and predictive value were lower than in other studies, which had used lower CD4 cut-offs previously [7,8].

A TLC cutoff of 1500 cells/mm³ would have a considerably high sensitivity (91.4%) in detecting patients with CD4 counts below 500 cells/mm³, but specificity and positive predictive value are quite low (40.2% and 39.5% respectively). Raising the TLC threshold to 2000 cells/mm³, the sensitivity falls to 78.1%, meaning ability to detect 8 in 10 patients in need of HAART, with an improved positive predictive value of 66.1%, implying that in every 10 patients with TLC levels below 2000/mm³, at least 6 will have a CD4 count of less than 500 cells/mm³. Further raising the TLC threshold lowers the sensitivity more without any meaningful improvement in the other parameters. To balance between the detection of patients qualifying for HAART and the burden of over-classifying people as requiring treatment, which includes side effects and increase cost to running of programmes, TLC cutoff of 2000 cells/mm³ seems to be the most suitable to predict CD4 counts of below 500 cells/mm³. The correlation coefficient between TLC and CD4 count was strongly positive (r=0.582, p<0.001); similar results reported in other studies [2,7,13]. However in our study, the correlation between haemoglobin level and CD4 count was weak (r=0.046, p=0.484), contrary to the findings elsewhere [14]. Such could probably be due to the fact that our study included patients already on care whether on HAART or not, with a high chance of continuing nutritional and medical care as opposed to new patients with coexisting burden of other infectious diseases and poor nutrition. The correlation between age and CD4 count in our study was significant (r=-0.344, p<0.001), contrary to findings elsewhere [7].

For CD4 less than 200 cells/mm³, which still is an important consideration in opportunistic infection prophylaxis, a TLC cutoff of 1500 cells/mm³ displayed a sensitivity of 31.4%, specificity of 91.5%, PPV of 61.1% and NPV of 75.8%. TLC cutoff of 1400 cells/mm³, was also reported elsewhere but with a higher sensitivity of 73% [9]. Other studies conducted in East Africa indicated better performance with higher cutoffs for detecting CD4 counts below 200/mm³. A TLC level of 2100 cells/mm³ was shown to best predict CD4 count of <200 cells/mm³

(sensitivity 83%, specificity 77%, PPV 92%, NPV 57%) as opposed to that of 1200 cells/mm^3 reported in a study from Uganda [15]. Sensitivity, specificity, PPV, NPV improved to 81%, 90%, 90% and 80% respectively with the raising of the TLC cutoff to detect CD4 count <200 cells/mm^3 from 1200 to 1900 cells/mm^3 in a study conducted in Kenya [10]. However, our study did not test the performance of these cutoffs above 1500 cells/mm^3. The higher cutoffs required in African settings as compared to WHO suggested cutoffs was suggested to be possibly due to background burden of infectious disease, because WHO recommendations were largely driven by findings from the western countries [16].

Some studies observed TLC to be an imprecise surrogate marker for predicting CD4 counts, but advised that it can still be used in resource limited settings with no cheaper or feasible alternative, like Kenya [17]. This is even of utmost urgency as Governments in sub-Saharan Africa prepare to take full control of HIV treatment programmes in their respective countries [1], remembering that even with massive support from donors like PEPFAR, more than half of these countries still reported ART coverage of less than 50% in 2010 [18]. Since our study included patients on HAART and those not on HAART, it provides useful preliminary information to not only initiate HAART but also to monitor patients already on treatment. However, an important weakness of the study was the fact that it was cross-sectional in nature therefore could not give more information on the behaviour of TLC as CD4 counts change in the course of treatment.

Conclusion and recommendations

The transition from donor funded to government driven HIV treatment programmes in sub-Saharan Africa has already started. With the state of health care systems in most of these countries, it is highly likely that the transferred patients will be devolved to level three or health centers for continuity of care. This level of the health system is characterized by considerable country-wide distribution but with meager financial, equipment and human resources. It is imperative that the relatively junior clinical staff in these centers is supported with cheaper and easy to use tool in readiness for this huge number of patients from the donor clinics and also occasioned by the revising upwards of CD4 cutoffs for initiating HAART. Our study indicated that a TLC cutoff of 2000 cells/mm^3 is efficacious in this respect and the same needs to be corroborated in further, larger studies with the new higher WHO treatment cutoffs of CD4 counts below 500 cells/mm^3.

Conflict of interest: The authors declare no conflict of interests.

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