Reviewer's report

Title: Utility of Total lymphocyte Count as a Surrogate Marker for CD4 counts in HIV-1 infected Children in Kenya

Version: 1 Date: 20 February 2011

Reviewer: Anand Reddi

Reviewer's report:

This is an interesting and well-written manuscript. Githinji et al. explored the use of total lymphocyte count (TLC) as an alternative to CD4 count and CD4% to monitor antiretroviral-naïve children in three HIV clinical sites in Kenya. The study is retrospective. The subject matter is interesting given that in many resource limited settings in Africa access to CD4 FACS machines is limited therefore making the ability to track HIV clinical progression with TLC an extremely useful alternative to CD4. The manuscript reports that increasing established World Health Organization TLC results in greater sensitivity but reduced specificity. The authors demonstrate that current WHO TLC thresholds would have missed 67-75% of children below the age of 5 in their cohort. The authors proposed higher TLC thresholds and provided a detailed and thoughtful analysis. However the author’s increased cutoff for TLC results in sensitivity values below 90% as well as lower positive predicative values. Good observations usually have a sensitivity of greater than 90%. The manuscript, despite some limitations, is an important contribution to the literature and will provided increased evidence for the WHO to consider revising their age-specific TLC thresholds.

- Major Compulsory Revisions

Abstract:

1. Please better define “severe immunosuppression” in the results section of the abstract. (A good definition could include WHO clinical staging or CD4 count %).

2. In the results section of the abstract please change the first sentence to read “>59 months of age (r=0.68, p<0.001).

Background:

1. Since this paper maybe read by clinicians not familiar with terms “sensitivity” and “specificity” in a public health context please provide at most two sentences with references describing these topics and their applicability to the monitoring HIV/AIDS clinical progression. This will allow for audiences who may not have biostatics expertise to greater understand your paper.

2. Please also define positive predicative value (PPV) and negative predicative value (NPV) in a public health context with references describing these topics and their applicability to monitoring HIV/AIDS clinical progression. This will allow for audiences who may not have biostatics expertise to greater understand your
3. Given that WHO TLC cut-off values were largely driven by data from US and Western European Cohorts please write a brief sentence or two describing that accepted clinical markers and values need to be population/geography specific given differences in populations. Ex. The need for region specific validation of CD4 and TLC changes on HAART and pre-HAART.

4. Please provide a brief explanation in background and discussion about the differences in cost between CD4 and TLC in the Kenyan context. Use US dollar values.

Results

1. Please include integration of WHO clinical staging into Table 3. Perhaps include an additional table where CD4 count, CD4%, and TLC also stratified with WHO staging. It would help justify the clinical relevance of TLC with disease progression and benefits of introduction of HAART.

Discussion:

1. Please elaborate on the fact that overall correlation between TLC and CD4% was weak (r=0.06) in the context that CD4% is more likely used in pediatric initiation of HAART when available versus CD4 count. Some readers maybe skeptical of the lack of association between TLC and CD4% and addressing this point will improve your manuscript.

1a. Include a discussion and explanation that some pediatric studies did not find a correlation between CD4% and antiretroviral regimen durability, clinical effectiveness, and survival suggesting that some studies suggest that CD4% is also not always an optimal predicative marker and thus an association between CD4% and TLC is not per se necessary. This will contrast your statement that in the background that “A meta-analysis by Dunn on a large group of children in US and Europe found TLC <2500 cells/mm^3 or CD4 percent <20% to be associated with high mortality.”

Please cite the following studies with your explanation/comments about CD4% as not being a useful predicator and provide comment:


1b. Cite studies that showed CD4% was beneficial as a predicator of therapeutic progress and mortality to provide a balanced picture of lack of association between CD4% and TLC and potential implications.

2. Please include discussion taking multiple measurements of TLC at more frequent intervals may reduce variability and have the potential to improve predicative accuracy (Mahajan AP et al., JAIDS, 2004, Changes in Total Lymphocyte Count as a Surrogate for Changes in CD4 Count Following Initiation of HAART: Implications for Monitoring in Resource-Limited Settings.) Mahagjan
AP et al. report “Thus while a single TLC measure has good prognostic properties for predicating direction of change in CD4, it maybe less reliable as proxy for the actual CD4 change” thus suggesting the utility of multiple measurements.

3. Please provide a brief explanation in background and discussion about the differences in cost between CD4 and TLC in the Kenyan context. Use US dollar values.

4. Please include a discussion that if TLC decreases the direction of CD4 count change is not easily predicated as a potential reason for not using TLC in clinical practice (Mahajan AP et al., JAIDS, 2004). Should be in limitations section of discussion.

5. Also include a discussion about if TLC count could be appropriate in the context of HIV co-infection such HIV/TB co-infection given the high prevalence of leukocytosis. Also should be in potential limitations sections. Additionally, see if papers exist on this topic and how that might impact your study or contribute to possible limitations and cite.

6. Please include a brief section that these data suggest that the WHO should consider revision and further research of its current TLC guidelines. Further identify limitations that preclude your proposed cutoffs as guidance until further research is available with studies developed with greater power and do not have limitations of a retrospective study.

7. Please include the following citation in your discussion with appropriate textual evidence to strengthen your manuscript.


8. Please also consider a brief discussion of the seminal Lancet 2010 study by the DART Trial Team-Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomized non-inferiority trial and the potential implications on TLC given the context of virologic failure and antiretroviral resistance and the need to study TLC in these adverse clinical contexts.

Tables/Figures

1. The units and axis in Figure 1 did not show up well on my manuscript pdf. Please improve quality and font size for clearer reading.

- Minor Essential Revisions

1. Please include a period after HAART and before Stated differently. “As a good surrogate marker the TLC cut-off values should be highly sensitive in identifying children of low CD4 count requiring HAART. Stated differently, …”
- Discretionary Revisions
1. Stratify CD4 Count, CD4%, and Total Lymphocyte Count by WHO Status might be helpful.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.