Evaluation of Relationship Between CD4 and Total Lymphocyte Count in Children with HIV

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Abstract

■BACKGROUND: CD4 counts and viral loads are integral components of HIV disease monitoring, allowing decision-making regarding treatment initiation and changes. However these technologies are costly and require lab equipment and expertise that is not available in many resource-poor settings. There is a paucity of data regarding the correlation between CD4 and TLC in HIV-infected children. However, based on limited data, the WHO has made recommendations regarding TLC cut-offs for initiation of anti-retroviral treatment for children. Using our database of children with HIV, we attempted to further evaluate the relationship between CD4 and TLC in order to inform current practice in HIV disease management in resource-limited settings.

■METHODS: We retrospectively reviewed clinical and laboratory data of all HIV-infected children seen at The Hospital for Sick Children from 1995 – 2005. Using paired CD4-TLC data for each patient, we determined the degree of relatedness between these two measures, taking into account potential confounders such as age, antiretroviral treatment and race. We evaluated the reliability of the TLC cut-offs suggested in the WHO 2006 guidelines on pediatric ART in resource limited settings.

■ RESULTS: Data for 126 patients aged 2 weeks to 18 years were collected, including information from 3667 visits. There was no significant difference in TLC count between children of black race and children of other races. In regression analysis adjusted for age, race, and antiretroviral treatment, TLC and total CD4 count were highly correlated (P<0.0001) as were change in TLC and change in CD4 count (p<0.0001). A mean change in TLC of 2.0 x106 cells/L (SE 0.038) was observed for every 1 cell/mm3 change in CD4 count. In evaluating the cut-offs proposed by WHO, the TLC cut-off for each age group (<1, 1-3, 3-5, 5-8, and >8 years) predicted the appropriate CD4 cut-off in 80%, 88%, 83%, 84%, and 89% of the time, respectively.

■ CONCLUSIONS: TLC is a good predictor of CD4 count, though the cut-offs for treatment proposed by the WHO may be suboptimal.

Background & Rationale

CD4 counts and viral loads are integral components of HIV disease monitoring, allowing decision-making regarding treatment initiation and changes. Unfortunately, these technologies are expensive and require expertise and lab equipments making them unrealistic in many resource-poor settings where the majority of HIV-infected individuals reside.

Multiple studies have shown good correlations between CD4 cell counts and total lymphocyte counts (TLC) in adults[1,2], making this a viable option for interim HIV management when resources are scarce. The WHO has released guidelines for management of children with HIV in resource-poor settings[3] with recommendations for cut-offs for TLC with respect to treatment initiation in children with asymptomatic or mildly symptomatic disease (Tables 1 & 2). WHO guidelines for adults suggest a TLC cut-off for treatment initiation of 1200 cells/mm^3.[4]

Few studies have been published in the literature evaluating the correlation between CD4 count and TLC in children[5,6]. Evaluating this relationship is complicated by the fact that, unlike in adults, CD4 counts in children vary with age. In addition, recent literature suggests that there may be racial differences in normal CD4 counts, with black children having lower normal CD4 counts for age than Caucasian children[7].

We attempted to evaluate the relationship between CD4 count and TLC by utilizing the database from our HIV clinic at the Hospital for Sick Children. In addition, we evaluated the cut-offs suggested by the WHO to see how well these recommendations would have predicted actual treatment thresholds for CD4 counts in our clinic population.

REFERENCES: 1.Kumarasamy, *JAIDS,* 2002; 2. van der Ryst et al, *JAIDS,* 1998; 3. WHO – Antiretroviral Therapy of HIV infection in Infants and Children in Resource-Limited Settings – Toward Universal Access, 2006; 4 WHO – Scaling Up Antiretroviral Therapy in Resource-Limited Settings – Treatment Guidelines for a Public Health Approach, 2003; 5. Mofenson et al, *Lancet*, 2003; 6. HIV Paediatric Prognostic Markers Collaborative Study Group, *Lancet*, 2005; 7. European Collaborative Study, *PIDJ*, 2005.

Methods

We retrospectively reviewed clinical and laboratory data of all HIV-infected children seen at The Hospital for Sick Children from 1995 – 2005. Using paired CD4-TLC data for each patient, we determined the degree of relatedness between these two measures using mixed linear regression analysis accounting for repeated measure, controlling for potential confounders such as age, antiretroviral treatment and race.

We also evaluated the reliability of the TLC cut-offs suggested in the WHO 2006 guidelines on pediatric ART in resource limited settings and 2003 guidelines on adult ART (using the TLC cut-off of 1200 for children over 8 years). Percentage of time when guidelines correctly predicted treatment threshold was determined using all paired data. ROC curves were calculated to determine ideal cut-offs for CD4 counts and CD4 percentages using averaged values of TLC, CD4 and CD4 percentage for each subject with all available data points in each age group.

Tables 1 & 2: WHO recommendations for CD4 & TLC cut-offs

Table 1. TLC criteria for severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 and where CD4 measurement is not available

Immunological marker^a	Age-specific recommendation to initiate ART^b [C (II)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	5 to 8 years^c
TLC	<4000 cells/mm^3	<3000 cells/mm^3	<2500 cells/mm^3	<2000 cells/mm^3

Table 2. CD4 criteria for severe HIV immunodeficiency

Immunological marker^a	Age-specific recommendation to initiate ART^b [A (I)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	≥5 years
%CD4+^{c}	<25%	<20%	<15%	<15%
CD4 count^c	<1500 cells/mm^3	<750 cells/mm^3	<350 cells/mm^3	<200 cells/mm^3

Results

Demographics

■ Data were available from 126 HIV-infected children beginning as young as 14 days up to 19 years of age. Of data from 3667 visits, complete data was available in 2781 visits.

■ An average of 27 (sd 17) data pairs were available for each patient, with a range from 1 to 69 data pairs.

■ 57% of children were Afro-Caribbean; 28% were Caucasian; 14% were Asian; and 2% were Latino.

■ 79% received HAART at some point in the study period, starting at a mean age of 7.2 years (sd 5.3).

■ 53% of data pairs were from when children were on HAART, 32% when on mono- or dual-therapy, and 15% when on no antiretroviral therapy.

Relationship Between TLC and CD4 in Children

■ Regression analyses adjusted for age, race, and antiretroviral treatment found a significant relationship between
- TLC and total CD4 count (P<0.0001) depicted below (Figure 1)
- Change in TLC and change in CD4 count (p<0.0001)
- Change in TLC and change in CD4 percentage (p<0.0001)

■ A mean change in TLC of 2.0 x10^6 cells/L (SE 0.038) was observed for every 1 cell/mm^3 change in CD4 count.

■ Age and treatment had significant associations with TLC in all three analyses.

■ Race had a significant effect on the relationship between change in TLC and change in CD4 count (with average TLC change in black children being less than in Caucasian/Asian children). This effect was not seen in the other two analyses (TLC and CD4 count; change in TLC and change in CD4 percentage).

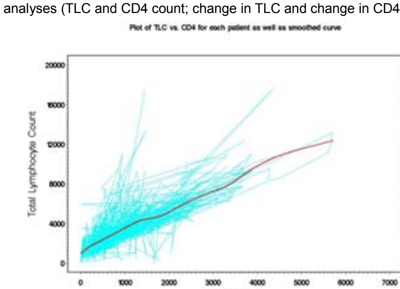


Figure 1: TLC vs CD4 count regression curve

Evaluation of WHO Cut-offs

■ The WHO TLC treatment criteria for the age groups <1, 1-3, 3-5, 5-8, and >8 years correctly predicted the appropriate CD4 cut-off in 80%, 88%, 83%, 84%, and 89% of cases, respectively.

■ ROC curves for TLC vs CD4 count are depicted below for each age group; similar curves were created comparing TLC cut-offs vs CD4 percentage cut-offs, which did not yield as robust relationships. The optimal TLC cutoffs derived from our data were similar to those of the WHO.

Figure 2: ROC – TLC vs CD4 (age <1y)
Best cut-off = 5235 cells/mm^3
N = 28
AUC = 0.85, CI (0.59 – 0.94)

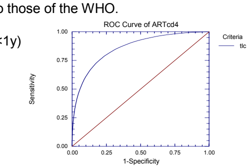


Figure 3: ROC – TLC vs CD4 (age 1-3y)
Best cut-off = 3298 cells/mm^3
N = 45
AUC = 0.75, CI (0.30 – 0.93)

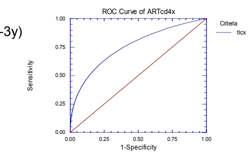


Figure 4: ROC – TLC vs CD4 (age 3-5y)
Best cut-off = 2200 cells/mm^3
N = 51
AUC = 0.99, CI (0.92 – 1.0)

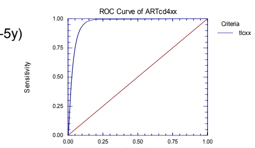


Figure 5: ROC – TLC vs CD4 (age 5-8y)
Best cut-off = 1370 cells/mm^3
N = 59
AUC = 0.96, CI (0.82, 0.99)

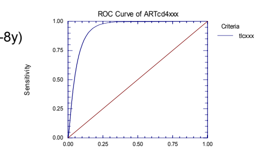
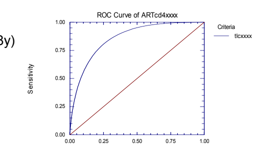


Figure 6: ROC – TLC vs CD4 (age>8y)
Best cut-off = 1018 cells/mm^3
N = 66
AUC = 0.89, CI (0.46 – 0.98)



Discussion

■ Our data suggest a strong relationship between TLC and CD4 count/ CD4 percentage in children with HIV infection. One of our analyses suggests a possible effect of race on this relationship; this warrants further examination.

■ The WHO TLC cut-offs for treatment initiation agree reasonably well with the data collected from our patient population (80-89% of cases). Likewise, the TLC cut-offs yielded good ROC curves, although the ideal cut-offs from our curves were slightly higher in the younger age groups and slightly lower in the older age groups.

■ Some of the variation in our findings compared with WHO guidelines could be attributed to the fact that our data came from repeated measures of a relatively small number of patients. As well, 53% of our data came from children already taking HAART, whereas the cut-offs were designed for use in children not yet on therapy and were derived directly from longitudinal survival data.

■ Further evaluation of TLC cut-offs for resource-limited settings is warranted, with a focus on both treatment initiation decision-making as well as treatment monitoring.