Published in final edited form as:

Pediatr Infect Dis J. 2010 October ; 29(10): 966–968. doi:10.1097/INF.0b013e3181e0554c.

CD4 cell count criteria to determine when to initiate antiretroviral therapy in Human Immunodeficiency Virus Infected children

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Abstract

We evaluated the validity of CD4 count against CD4 percentage criteria of 2008 World Health Organization guideline for initiating antiretroviral therapy using the data of 446 Asian HIV - infected children aged 1 to 12 years who were screened to the PREDICT study. The overall sensitivity and specificity were 34% and 98%, respectively. Using the current CD4 count criteria would globally result in 66% missed opportunity to initiate treatment in a timely fashion. Raising CD4 count thresholds should be considered to increase its sensitivity and reduce missed opportunity.

Keywords

HIV; CD4; antiretroviral treatment; ART initiation; WHO; children; Asia

Introduction

Access to antiretroviral treatment (ART) has led to a dramatic decrease in morbidity and mortality for HIV-infected children worldwide¹. Both CD4 percentage (CD4%) and absolute CD4 count are established in treatment guidelines as thresholds for ART initiation. Large cohort studies have shown that CD4% is less variable and less age-dependent than absolute CD4 count in early life^{2,3}; therefore, CD4% is preferred in treatment guidelines for children younger than 5 years of age.⁴⁻⁶ However, the main obstacle to perform CD4% in

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some resource-poor settings is the unavailability of dual platform flow cytometry.⁷ CD4 count can be measured using single platform flow cytometry or other methods that require less expensive equipments and without the need to perform complete blood count.⁷

Among children who had severe symptoms or developed clinical AIDS, the ART should be initiated promptly regardless of CD4 level. For children with mild or moderate symptoms, CD4-guided threshold based on age is considered to make a decision for ART. Antiretroviral therapy initiation thresholds for children ages 12 months and older vary among guidelines.⁴⁻⁶ (table 1) Risk of HIV disease progression to AIDS is predicted by both CD4% and CD4 count³ and is highest in younger children. The 12-month AIDS risk for children having CD4 < 20% at ages 1, 2, 5 and 10 years are 21%, 12%, 4.7% and 2.2% respectively.² This emphasizes the importance of correct criteria for starting ART especially among younger children with the highest risk for AIDS. Missed opportunity to start ART among those who need treatment the most could be devastating. Here we investigate the sensitivity and specificity of CD4 cell count as compared to CD4% criteria according to the 2008 WHO guidelines in deciding when to initiate ART in a cohort of HIV-infected Thai and Cambodian children with mild and moderate symptoms.

Methods

This study utilized demographic data and CD4 information from the screening visit of 446 children who underwent screening procedures for the Pediatric Randomized of Early vs. Deferred Initiation in Cambodia and Thailand study (PREDICT study, identification number NCT00234091) conducting at 7 hospitals in Thailand and 2 hospitals in Cambodia between March 2006 to September 2008. The study aimed to recruit 300 ART-naïve children 1–12 years of age with CD4 15–24% and without severe HIV symptoms. They were then randomized to starting ART at CD4 15–24% vs. deferring until CD4 declined to below 15%. The study was approved by national and local institutional review boards in Thailand and in Cambodia. All guardians gave informed consent.

At the screening visit, medical history taking, physical examination and laboratory testing (complete blood count, CD4%, CD4 count and chemistry) were performed. CD4% was measured by dual platform flow cytometry with FACS Calibur/FACSCAN (Becton Dickinson, CA, USA) used in 8 sites and Coulter (Beckman Coulter, CA, USA) in 1 site. CD4 count was calculated [Total lymphocyte count × CD4%]. All laboratories passed the US National Institutes of Health Division of AIDS inspection and the UKNEQAS proficiency testing. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are stratified by age groups. We also calculated changes in the risk of missed opportunity to start ART (100 – sensitivity) as the CD4 count threshold increased. Data analysis was performed with Stata Version 11 (Statacorp, College Station, Tx).

Results

Four hundred and forty-six children screened for the PREDICT study were included in this analysis. The median (IQR) age was 76 (47 – 104) months, 59% were female, 58% were Thai and 42% were Cambodian. The percentage of children fitting the US Centers for Disease Control and Prevention (CDC) clinical category N (no symptoms), A (mild symptoms), B (moderate symptoms) were 3%, 65% and 33% respectively. The mean (SD) of CD4%/CD4 count was 19.8(6.6)/1168 (618) for children ages 12–35 months (n=69), 20.8(6.9)/821 (386) for 36–59 months (n=93) and 19.6 (6.4)/592 (330) for ≥ 60 months (n=284). Forty seven percent, 41% and 18% had CD4% that fit the WHO initiation criteria in the three age groups respectively. Sixty eight of 146(46%) children failed screening

because they had $CD4\% < 15\%$, 67 children (46%) had $CD4 > 25\%$ and 11(8%) due to abnormal chemistry laboratory results.

In Table 2, we assessed the usefulness of CD4 count when compared to CD4% using the WHO 2008 criteria for ART initiation for all children. When all children were included, CD4 count criteria had 34% sensitivity and 98% specificity in identifying children who need ART. The overall sensitivity of CD4 count when compared with CD4% to identify children who need ART was low regardless of the age of the child and would have resulted in 66% missed opportunities to start ART. We then assessed in three age groups the predictive values for the different CD4 count thresholds compared with the current WHO recommended thresholds (< 750 , < 350 and < 200 cells/mm³ for children ages 12–35, 36–59 and 60 months respectively). We showed that sensitivity increased in all age groups when the CD4 count thresholds were raised while the specificity decreased. The latter decreased most dramatically in the youngest age group. When compared with the current WHO CD4 count thresholds, the 12–35 months old children had 24 and 69 percent reductions in missed opportunity to start ART when CD4 count thresholds were raised to 1000 and 1500 cells/mm³ respectively. Similarly, in those ages 36–59 months, reductions of 28 and 66 percent were seen with CD4 count thresholds of 500 and 750 cells/mm³ respectively. In the children 60 months of age, raising CD4 count thresholds to 350 and 500 cells/mm³ reduced the risk of missed opportunity to start ART by 46 and 80 percent, respectively.

Discussion

Using CD4% as the gold standard, we found that CD4 count had poor sensitivity for deciding when to start ART in Thai and Cambodian children >12 months of age with mild and moderate symptoms. Using CD4 count alone would have resulted in missing 66% of children who would have met treatment criteria using CD4%. However, the missed opportunities significantly reduced when the CD4 count threshold was raised especially among children above 5 years of age. This raises an important point that the CD4 count criteria according to the 2008 WHO guidelines are likely too low and need to be re-evaluated.

Initiation criteria using CD4% has generally been considered superior to using CD4 count because of the natural decline in CD4 count especially in early life.² Poor to fair correlation between CD4% and CD4 count especially in young children have been reported^{3,8} and raised the need for further investigations to define the CD4 count to initiate ART across age groups.⁹ Our data showed that the agreement between CD4% and CD4 count was modest and when we raised the CD4 count criteria, the sensitivity of CD4 count compared with CD4% improved in all age groups. Raising the CD4 count threshold to 1000 cells/mm³ in 12–35 months, 500 cells/mm³ in 36–59 months and 350 cells/mm³ in 60 months would resulted in a sensitivity around 53–67% without significant compromising the specificity. Large cohort analysis suggest that children age 5 years or older have similar HIV disease progression rate as young adults, and that similar CD4 count criteria for ART initiation can be used in both groups.⁸ According to the WHO rapid advice for antiretroviral guideline 2009/2010 among HIV-infected adults, the recommended CD4 threshold is below 350 cells/mm³¹⁰. When we apply this recommendation to data from children older than 60 months, the sensitivity to detect children who should initiate ART is significantly increase from 39% to 67%. The specificity decreased significantly in the youngest age group as CD4 count threshold rose likely as a result of the wide variability in CD4 count among children in this age group.

The strength of this study is that it reflects a real life clinical practice among HIV-infected children with mild and moderate symptoms who need CD4 to make decision of when to

initiate treatment. Children who had severe symptoms or clinical AIDS are not included because the decision to initiate ART is based upon clinical criteria. We also documented the increase of sensitivity of CD4 cell count based on new WHO guideline 2009/2010. The limitation of this study is that 36% of the study population are younger than 5 years which is the group with the highest variability in CD4 cell count.

Our data supports further investigation of the validity of 2008 WHO CD4 count criteria to initiate ART in children >12 months of age. Improving access to CD4% determination and re-evaluating the current CD4 count criteria are important to assess correctly when to start ART in HIV-infected children in resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The PREDICT study is sponsored by National Institute of Allergy and Infectious Disease (NIAID), Grant number U19 AI053741, [Clinical trial.gov](http://ClinicalTrials.gov) identification number NCT00234091, and co-funding by the National Research Council of Thailand. ART for PREDICT is provided by GlaxoSmithKline, Boehringer Ingelheim, Merck, Abbott and Roche. We thank Dr. Annette Sohn for her input on the manuscript. Please see SDC Appendix for the PREDICT Study Team.

Disclosure of funding: The study is sponsored by National Institute of Allergy and Infectious Disease (NIAID), Grant number U19 AI053741, [Clinical trial.gov](http://ClinicalTrials.gov) identification number NCT00234091, Antiretrovirals are provided by GlaxoSmithKline, Boehringer Ingelheim, Merck, Abbott and Roche.

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Table 1

Summary of recommended CD4 threshold for antiretroviral treatment initiation among HIV-infected children

Age	WHO 2008 ⁴	US 2009 ⁵	PENTA2009 ⁶
1–3 year	<20% or 750 cells	<25%	<25% or 1000 cells
3–5 year	<20% or 350 cells	<25%	<20% or 500 cells
>5 year	<15% or 200 cells	< 350 cells	< 350 cells

Table 2

The validity of CD4 cell count thresholds against CD4 percentage according to 2008 WHO Guidelines to initiate antiretroviral therapy in children

Age (N)	CD4% threshold	CD4 count threshold (cell/mm ³)	Sensitivity	Missed opportunity to start ART ^I	Specificity	PPV	NPV
Over all (N=446)			34	66	98	85	80
12–35 mo (n=69)	< 20%	< 750	38	62	87	71	62
		< 1,000	53	47	65	57	62
		< 1,500	81	19	27	49	63
36–59 mo (n=93)	< 20%	< 350	24	76	100	100	65
		< 500	45	54	98	94	72
		< 750	74	26	73	65	80
60 mo (N=284)	< 15%	< 200	39	61	99	91	89
		< 350	67	33	87	52	93
		< 500	88	12	68	36	96

Note :

^I Missed opportunity to start ART calculated by 100-sensitivity, PPV, positive predictive value; NPV, negative predictive value