Utility Of An Algorithm Of Surrogate Markers For CD4 Count To Determine Eligibility For HAART Among HIV Infected Pregnant Women.

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Background

- CD4 Count is a marker of HIV disease progression and consensually accepted as a marker for decision-making in the management of HIV/AIDS.
- However CD4 Count testing not readily available in developing countries.
- The WHO recommends use of Total Lymphocytes (TLC) in low resource settings. Studies done on non-pregnant populations indicate that TLC cut-off of 1200cells/mm³ is not an accurate predictor of CD4 count <200cells/mm³.
- Pregnant women should start HAART when CD4 count is <350cells/mm³.The WHO has not recommended a TLC threshold for this level of immunity.
- In light of expanding Prevention of Mother to Child Transmission (PMTCT) services there was need for affordable and reliable markers to inform decision-making in ART among pregnant women in poor resource settings.

Objectives

- To determine the correlation of surrogate markers'; TLC, Haemoglobin level (HB), Body Mass Index (BMI) and the WHO Clinical Stage (WCS) with CD4 Count.
- Calculate the optimal cut-off points for CD4 count < 350cells/mm³.
- Develop clinical algorithms that can be used as proxy for CD4 Count <350cells/mm³.

Methods

Study design and population:
- Retrospective analysis of cross-sectional data from randomly selected charts of HIV positive, ARVs naive pregnant women attended between January 2005 and November 2010.

Study site:
- The AMPATH centre PMTCT clinic of the USAID- Academic Model Providing Access to Healthcare (AMPATH) in western Kenya.

Analysis:
- Correlation and optimal cut-off points were calculated using the Pearson's Correlation and Linear regression.
- Sensitivity, specificity, positive predictive value(PPV), negative predictive value (NPV) were calculated and these values used to compute area under the Receiver Operating Curve (ROC) to determine their predictive accuracy.

Results

- Of 362 HIV infected women, 160 (44.5%) had CD4 Count <350cells/mm³ and 202 (55.5%) had CD4 Count >350 cells/mm³.
- The optimal cut-off points for TLC, HB, BMI were 850cells/mm³, 8.4g/dl and 15.5kg/m² with sensitivity and specificity of (8% and 97%), (17.4% and 92.5%) and (3.7% and 100%) respectively.
- The correlation between CD4 Count and TLC was significant at p< 0.01 (Pearson's Correlation= 0.192).

Table 1. Different cut-offs against CD4 Count < and > 350 cells/mm³

Variable	Overall	CD4 Count in Cell/mm³		OD (95% CI)	P value
		<350	>=350		
WHO stage					
I	277 (76.5%)	101 (63.1%)	176 (87.1%)	1.0	
II	35 (9.7%)	24 (15.0%)	11 (5.5%)	3.8(1.8-8.1)	0.001
III	48 (13.3%)	34 (21.3%)	14 (6.9%)	4.2(2.2-8.3)	<0.001
IV	2 (0.6%)	1 (0.6%)	1 (0.5%)	1.7(0.1-28.20)	0.696
Total lymphocyte count					
<1200	37 (10.2%)	26 (16.3%)	11 (5.4%)	4.8 (2.0-11.6)	0.001
1200- < 3000	261 (72.1%)	113 (70.6%)	148 (73.3%)	1.6 (0.9-2.8)	0.129
≥3000	64 (17.7%)	21 (13.1%)	43 (21.3%)	1.0	
Total lymphocyte count					
<1200	37 (10.2%)	26 (16.3%)	11 (5.4%)	1.0	
>=1200	325 (89.8%)	134 (83.8%)	191 (94.6%)	4.8(1.6-7.1)	0.001
HB level in g/dl					
≤ 10	108 (29.8%)	61 (38.1%)	47 (23.3%)	2.0(1.3-3.2)	
>10	254 (70.2%)	99 (61.88%)	155 (76.7%)	1.0	0.002
BMI in kg/m²					
<16.9	14 (3.9%)	9 (5.6%)	5 (2.5%)	2.5 (0.8-7.5)	0.115
17–18.4	22 (6.1%)	13 (8.1%)	9 (4.5%)	2.0 (0.8-4.7)	0131
>18.5-24.9	326 (90.0%)	138 (86.3%)	188 (93.0%)	1.0	

- Using Linear regression CD4 Count of <350cells/mm³ was best predicted by TLC of 850 cells/mm³. The sensitivity and specificity were 8% and 97% respectively.
- HB and BMI had a less significant positive correlation with CD4 count at p<0.01 (Pearson's Correlation= 0.184) and p<0.05 respectively.
- The algorithm of WCS II&III, TLC≤ 1000 and HB≤12g/dl in that order was the most optimal with 86% sensitivity, 92% specificity, 94% PPV, 74% NPV, 78% Youden's index (J) and 89% ROC.

Figure 1. Correlation between CD4 Count and TLC cells/mm³
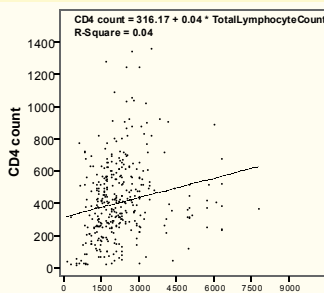
- The model was based on the premise that any HIV infected pregnant woman in clinical stage II & III was likely to be eligible for HAART and more so if they had TLC ≤1000 and / or HB≤12g/dl.
- However only 39 subjects met this criterion out of the 58 who had WCS II&III. The model failed to account for the subjects classified as WCS I disease that in fact had CD4 Count < 350 cells/mm3.

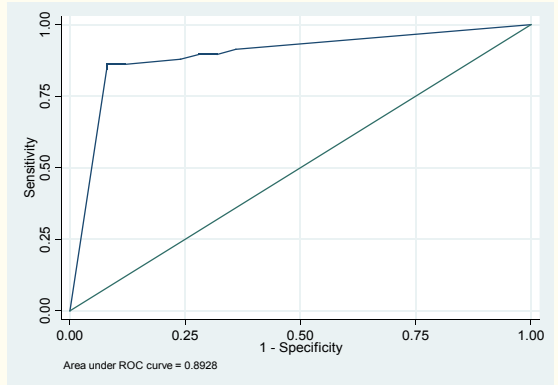### Figure 2: ROC Curve for WCS II & III, TLC≤1000, HB≤12

Area under ROC curve = 0.8928

Table 2: Different algorithms

Algorithm	CD4 cell counts/mm³		Population	Sensitivity	Specificity	PPV	NPV	AUC	J
	<350	>=350							
WCS II& III	58	25	83	36.48%	87.56%	69.9%	63.5%	0.6202	0.24
WCS II & III, TLC<=1000	11	2	13	6.92%	99%	84.6%	57.3%	0.5296	0.06
WCS II&III, TLC<= 2000	32	8	40	20.13%	96.02%	80.0%	60.3%	0.5807	0.16
WCS II& III, TLC <=1000,HB<12	9	2	11	5.66%	99.00%	81.8%	57.0%	0.5233	0.05
WCS II&III, TLC <=2200,HB< 12	33	5	38	20.75%	97.51%	86.8%	60.9%	0.5913	0.18
WCS II& III,TLC<=2200,HB<12, BMI<18.5	7	2	9	4.38%	99.01%	77.8%	56.7%	0.5169	0.03
WCS II&III,TLC<=2200,HB<10, BMI<18.5	5	1	6	3.13%	99.50%	83.3%	56.5%	0.5131	0.03
WCS II&III,TLC<=2000,HB<8, BMI<18.5	2	0	2	1.25%	100.0%	100.0%	56.1%	0.5063	0.01
TLC<1000,HB<12	13	7	20	8.13%	96.5%	65%	57%	0.5233	0.05
TLC<1700,HB<12	54	33	87	33.75%	83.66%	62.1%	61.5%	0.5871	0.17
TLC<1000,HB<10	7	3	10	4.38%	98.51%	70.0%	56.5%	0.5144	0.03
TLC<3000,HB<10	54	36	90	33.75%	82.18%	60.0%	61.0%	0.5796	0.16
WCSI,HB<12,TLC<3000	63	80	143	62.38%	54.55%	44%	72%	0.5846	0.17

Conclusion

- TLC, HB, BMI and WCS have low predictive accuracy for CD4 Count < 350 cells/mm³ despite having a positive correlation with CD4 Count.
- Combination of markers increased the sensitivity only marginally but lowered specificity at all TLC thresholds.
- Their predictive value was limited when used in algorithm to identify pregnant women eligible for HAART.
- All markers identified those eligible for HAART when low thresholds were used as indicated by very high specificity obtained.

Recommendations

- TLC, HB, BMI and WCS are clearly predictors of immune deterioration and advanced disease.
- However have limited predictive value in identifying pregnant women eligible for HAART.
- More global efforts should be made to provide CD4 Count testing in low resource settings.

Acknowledgements

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- AMPATH/ Moi University, Eldoret Kenya.
- Moi Teaching and Referral Hospital, Eldoret Kenya.

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