Field testing of World Health Organization (WHO) 2003 recommendations for initiating anti-retroviral therapy (ART) where CD4 is not available revealed low sensitivity among Stage I and II patients; a combination of Automated Total Lymphocyte Count (TLC) and Haemoglobin (Hgb) can ration the referral for CD4 testing

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Background

Many regions lack access to CD4 testing which may limit appropriate access to ART. Where CD4 testing is unavailable the 2003 WHO guidelines recommend initiating ART among Stage III and IV patients and among Stage II patients with a TLC<1200cells/ml.

Objectives

To assess the field performance of WHO recommendations specifically on Stage I or II patients and explore alternate models for initiating ART or rationing CD4 testing based on TLC and Hgb.

Methods

An analysis was conducted using anonymous patient data from projects in Nchelenge, Zambia; Lagos, Nigeria; and South Kivu, DRC. Eligibility for ART according to 2003 WHO guidelines using clinical stage and TLC was compared to CD4 based criteria. Various TLC and Hgb thresholds were examined to optimize sensitivity and specificity among Stage I and II patients for detecting a CD4≤350.

Results

468 ART naive subjects (98 from DRC, 217 from Nigeria, 153 Zambia) had CD4 and TLC measurements within 6 months of entry into the study. Two hundred and twenty one (47%) had a CD4≤200 and 325 (69%) had a CD4≤350. 49% of patients with a CD4<350 had TLC<1200.

The sensitivity and specificity of the 2003 WHO recommendations among Stage I and II patients for detecting a CD4≤350 was 9% and 99%, respectively. Including all Stage I patients with a TLC<1200 improved sensitivity by 37% (allowing 43% of patients to be correctly identified), with only a 7% drop in specificity. A model utilizing a TLC<1400 combined with a cut off of Hgb<11 to rule in subjects with an intermediate TLC between 1400 and 1900 provided optimal accuracy, capturing 83% of those with a CD4≤350. This model also had a 100% sensitivity for detecting patients with a CD4≤200.

Conclusions

This analysis shows that many patients in Sub-Saharan Africa present for HIV care when they are still asymptomatic, and up to 69% of these at baseline have CD4 counts in the range where ART is indicated. The 2003 WHO guidelines performed very poorly with respect to identifying stage I or II patients eligible for ART based on a CD4 count criteria of ≤350 or ≤200 (sensitivity of 9% and 11% respectively). For our study population, if CD4 testing were not available, recommending ART for both stage I and II patients with a TLC<1200 would result in five fold increase in the number of these patients receiving ART (160 vs. 31) with a minimal increase in the absolute number of patients started on ART with a CD4>350 (11 vs. 1).

For regions where CD4 testing is available but access is limited by distance or cost, baseline CD4 testing could be restricted to those in Stage III, IV, and those in Stage I or II with a TLC<1400 or those in Stage I or II with an intermediate TLC (1400 - 1900) and a Hgb<11.

In our study population, by using this method 100% of those in Stage I or II with a CD4≤200 would receive CD4 testing as would most of those with a CD4≤350. In this way, only 54% (204/375) of Stage I or II patients would require baseline CD4 monitoring resulting in a significant reduction in the total utilization of CD4 testing.

Due to the lack of precision of manual TLC measurements, the conclusions of this study are limited to those sites with access to automated TLC testing.

This analysis reinforces the need for improved access to CD4 testing to HIV positive patients living in SSA and demonstrates the shortcomings of the current 2003 WHO recommendations.

Table 1. Stage stratified by CD4

	CD4 ≤200	200<CD4≤350	CD4>350	Total
Stage I	160	79	121	360
Stage II	61	25	22	108
Stage I or II	221	104	143	468

Table 2. CD4, TLC, and Hgb summaries and correlation with CD4 among Stage I and II patients.

	CD4	TLC	HgB
Median (IQR)	203 cells/ml (88-371)	1500 cells/ml (1000-2090)	10.5 g/dl (9.0-11.6)
Correlation with CD4	1.0	0.38	0.16

Table 3. Comparison of CD4 based criteria for initiating ART with various TLC based criteria among Stage I and II patients (N=468).

	Starting ART	CD4≤350	CD4>350	Sensitivity	Specificity	PPV	NPV	accuracy
Total		**325**	**143**					
CD4 ≤ 350 based	325	325	0	1.00	1.00	1.00	1.00	1.00
WHO 2003 (Stage II & TLC<1200)	31	30	1	0.09	0.99	0.97	0.32	0.37
TLC < 1200	160	149	11	0.46	0.92	0.93	0.43	0.60
TLC < 1400	205	185	20	0.57	0.86	0.90	0.47	0.66
TLC < 1600	259	220	39	0.68	0.73	0.85	0.50	0.69
TLC < 1800	303	249	54	0.77	0.62	0.82	0.54	0.72
TLC < 1900	327	262	65	0.81	0.55	0.80	0.55	**0.73**
TLC < 2000	336	266	70	0.82	0.51	0.79	0.55	0.72
TLC < 2500	413	303	110	0.93	0.23	0.73	0.60	0.72
TLC < 3000	435	312	123	0.96	0.14	0.72	0.61	0.71

**Accuracy = (true positives + true negatives)/ (total number of patients)*

Table 4. Comparison of CD4 based criteria for initiating ART with various TLC and Hgb based criteria among Stage I and II patients (N=375).

					CD4≤200 cut off					CD4≤350 cut off				
	Starting ART	**CD4≤200**	**200<CD4≤350**	**CD4>350**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**accuracy**
Total		**168**	**91**	**116**										
TLC < 1200	120	90	22	8	0.54	0.86	0.75	0.69	0.71	0.43	0.93	0.93	0.42	0.59
TLC < 1200 or TLC [1200,2200)+hg<11	205	120	47	38	0.71	0.59	0.59	0.72	0.65	0.64	0.67	0.81	0.46	0.65
TLC < 2000	262	146	63	53	0.87	0.44	0.56	0.81	0.63	0.81	0.54	0.80	0.56	0.73
TLC < 2000 or TLC [2000,3000)+hg<11	307	158	76	73	0.94	0.28	0.51	0.85	0.58	0.90	0.37	0.76	0.63	0.74
TLC < 1400	157	104	37	16	0.62	0.74	0.66	0.71	0.69	0.54	0.86	0.90	0.46	0.64
TLC < 1400 or TLC [1400,1900)+hg<11	247	168	47	32	1.00	0.62	0.68	1.00	**0.79**	0.83	0.72	0.87	0.66	**0.80**