Clinical Features Are Poor Identifiers of Advanced HIV Disease in the Absence of CD4 Quantification

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BACKGROUND

Advanced HIV disease (AHD) is defined in adults as a CD4 T-lymphocyte count of <200 cells/μL or WHO stage 3-4[1], triggering a series of interventions to identify and treat opportunistic infections (OIs) and rapidly initiate ART. Access to CD4 count testing is declining as a 'test and treat' approach to HIV has been adopted, and clinical features increasingly relied on to guide OI screening. However, evidence to date shows that clinical assessment alone is unreliable in determining whether a patient has AHD: meta-analyses in 2014 and 2025 of 15 and 21 studies respectively found WHO staging does not accurately predict CD4 counts of <200 cells/μL, with pooled sensitivities of 60-61% and specificity of 72-73%[2,3]. We combined WHO staging with demographics, symptoms and signs, using weighted scoring to assess whether clinical features can identify patients with immunological AHD without the requirement for CD4 testing.

METHODS

Data were collected from a prospective cohort study of adults attending a clinic in Soweto, Johannesburg following a positive HIV test. A logistic regression model determined clinical features associated with CD4 count <200 cells/μL, then model coefficients used as weights to devise a clinical scoring system, calculating optimal cut off using the Youden index. This threshold was combined with WHO staging to identify a patient as having AHD by the WHO definition.

Clinical feature	N	Crude OR (95%CI)	Adjusted OR (95%CI)	Adjusted p-value⁺
Age (years): <20	10	**0.12 (0.02, 0.96)**	0.13 (0.01, 1.16)	
20-29	196	**0.58 (0.4, 0.83)**	0.65 (0.44, 0.97)	
30-39	300	1	1	0.068
40-49	160	0.98 (0.67, 1.44)	0.97 (0.64, 1.46)	
50-59	58	1.24 (0.71, 2.19)	1.09 (0.6, 2)	
≥60	9	1.35 (0.36, 5.14)	1.59 (0.31,8.04)	
Sex: Female	442	1		
Male	287	**1.9 (1.4, 2.58)**	**1.47 (1.05-2.05)**	**0.025**
Weight (kg): <50	64	1.41 (0.83, 2.39)	1.31 (0.73, 2.33)	
50-75	486	1	1	
75-100	142	0.58 (0.39, 0.86)	0.72 (0.47, 1.09)	0.283
≥100	33	0.58 (0.27, 1.22)	0.9 (0.41, 1.96)	
	Missing: 8			
Cough	194	**2.76 (1.96, 3.89)**	**1.95 (1.21, 3.16)**	**0.006**
	Missing: 2			
Diarrhoea	83	**2.49 (1.54, 4.03)**	1.53 (0.9, 2.59)	0.116
	Missing: 5			
Fever	131	**1.73 (1.18, 2.55)**	0.65 (0.39, 1.1)	0.111
	Missing: 3			
Lymphadenopathy: **Axillary**	34/492	**3.62 (1.65, 7.92)**		
Cervical	19/489	0.86 (0.34, 2.18)		
Inguinal	41/495	**3.59 (1.76, 7.34)**		
Night sweats	125	**1.99 (1.35, 2.94)**		
	Missing: 6			
Oral candidiasis	24	**3.83 (1.49, 9.81)**		
	Missing: 222			
Weight loss	292	**2.83 (2.07, 3.85)**	**1.97 (1.35, 2.87)**	**0.001**
	Missing: 4			
Total	**733**		**715**	

Table 1: Frequency of demographic and clinical variables; crude and adjusted odds ratios of association with CD4 <200 cells/μL. Final model adjusted for age, sex, weight, cough, diarrhoea, fever, weight loss: factors remaining significant outlined in red. ⁺Wald's test, Likelihood-Ratio Test

Assessment of clinical features alone would fail to identify over a third of patients with Advanced HIV Disease

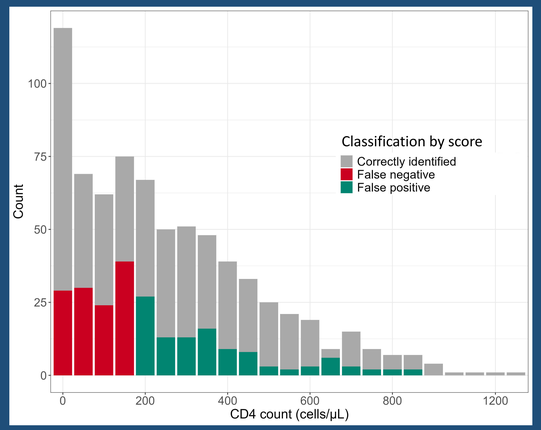


Figure 1: correct and misclassification of patients by WHO staging. N=711 with adequate data.

RESULTS

- Data were available for 733 participants: age range 17-73 years, 60% female (442/733), median CD4 count 231 cells/μL, 44% (325/733) had CD4 counts <200 cells/μL, 727/733 were not on ART.
- All assessed features were associated with CD4 <200 cells/μL on crude analysis (Figure 2). Following adjustment for associated characteristics, only cough, weight loss and male sex remained significantly associated with CD4 <200 cells/μL (Table 1).
- Stage 3-4 OIs were reported in 152 patients, with CD4 counts ranging from 1-828 (median 111 cells/μL).
- The final adjusted model included age, sex, weight, cough, diarrhoea, fever and weight loss, but was a poor fit for the diagnosis of immunological AHD, with pseudoR^2=0.09. Including WHO stage 3-4 OIs created a predictive model, with sensitivity (61%) and specificity (73%) for identifying patients with immunological AHD.
- Of 299 patients identified as having immunological AHD by the score, 109 (37%) had CD4 ≥200 cells/μL. Of those with CD4 <200 cells/μL, only 190/312 (61%) were identified by the model (Figure 1).

CONCLUSIONS

Clinical features are associated with CD4 count <200 cells/μL in patients with newly diagnosed HIV, but cannot reliably identify AHD, even when combined with WHO staging. Detailed recording and weighting of clinical features and OIs failed to improve the diagnostic accuracy of using WHO clinical staging for identifying immunological AHD, with similar sensitivity and specificity to previous meta-analyses[2,3]. A clinical scoring system without CD4 count resulted in underdiagnosis of AHD in around over a third of patients with low CD4 counts, and inappropriate diagnosis in over a third of patients with CD4 counts of >200 cells/μL.

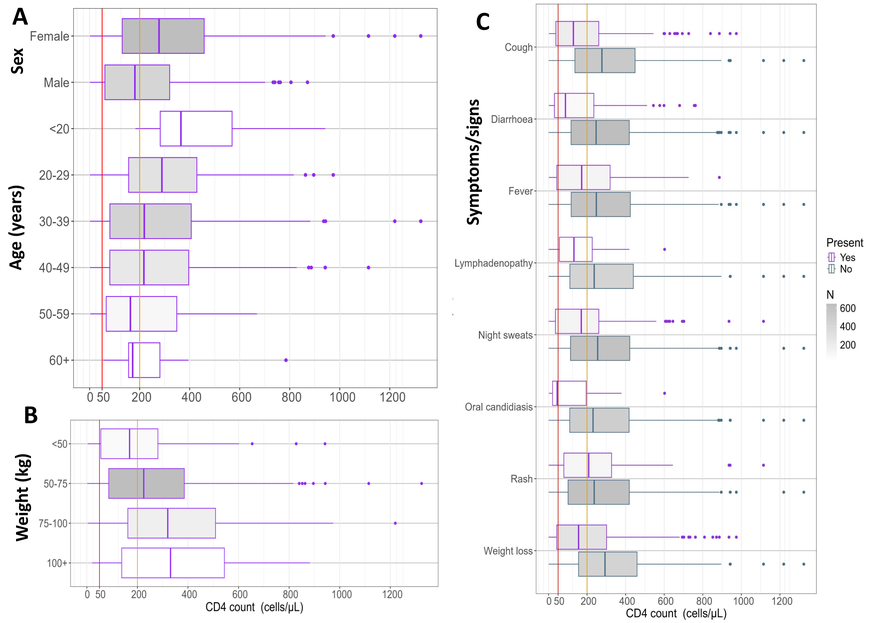


Figure 2: boxplot distributions of CD4 cell counts by sex and age category (A), weight (B) and symptoms/ signs (C). Orange vertical line demarcates threshold for Advanced HIV Disease (CD4 <200 cells/μL); red line demarcates threshold for very advanced HIV Disease (CD4 <50 cells/μL). Fill gradient represents increasing patient numbers.

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