

Non-virological criteria to predict virological failure in TAHOD and AHOD

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Objective

To systematically and comprehensively assess non-virological criteria (WHO and alternative) for treatment failure in TAHOD/ AHOD:

1. Can we improve performance?
2. Can we simplify use?
3. Can we optimize for use as a screening test for targeted viral load testing?

Methods

- Data
 - Patients in TAHOD/AHOD ≥ 6 months cART
 - All paired CD4 and viral load assessments (+/- 28d)
 - Virological failure defined as $>1,000$ copies/ml
 - CDC-C used as surrogate for WHO-4 (+/-TB; +/-PTB)
- Covariates
 - WHO 2006 clinical and CD4 criteria
 - Alternative clinical and CD4 criteria
 - Demographics, ARV class

Methods

Source	Covariate
2006 WHO non-virological criteria	<ul style="list-style-type: none"> WHO clinical stage 4 event Return of CD4 count to baseline value Fall of CD4 count greater than 50% of peak value CD4 count below 100 cells/μL after 12 months of ART.
Additional factors evaluated in previous studies	<ul style="list-style-type: none"> Percentage change in absolute CD4 count Any decline in CD4 count Change in CD4 count over the previous 6 months Change in CD4 count over the previous 12 months Change in total lymphocyte count Change in hemaglobin Previous use of mono/dual-therapy
Additional factors evaluated using Cox proportional hazards models	<ul style="list-style-type: none"> Gender Age HIV exposure category Baseline and time updated clinical disease stage Baseline and time updated CD4 count ART regimen (NNRTI-based/PI-based/other and first/subsequent) Cohort (TAHOD/AHOD).

Methods

- Logistic regression
- Model prediction assessed using sensitivity, specificity and area under ROC
- Sensitivity and specificity calculated
 - For all observations
 - For each patient, and then averaged across all patients to allow for the repeated measures data
- Multiple sensitivity analyses

Results

- 1,617 TAHOD patients
 - 8,086 paired CD4/VL data
 - 7.2% virological failure
- 1,022 AHOD patients
 - 16,164 paired CD4/VL data
 - 11.9% virological failure

Results

	Sensitivity	Specificity	AROC
WHO criteria: clinical and CD4			
Observations	29.5%	92.3%	0.609
Patients	24.1%	92.3%	0.582
WHO criteria: CD4 only			
Observations	28.9%	92.7%	0.608
Patients	23.2%	92.9%	0.581

- Little difference between TAHOD and AHOD
- Stable with increasing time since start of cART

Results

	Sensitivity	Specificity	AROC
Best model: WHO CD4 criteria, current CD4, CD4 change over and 12 months, age, exposure, ARV class			
Observations	25.2%	91.6%	0.582
Patients	22.9%	93.1%	0.580
Best CD4 model: WHO CD4 criteria, current CD4, CD4 change over 6 and 12 months			
Observations	22.1%	90.2%	0.561
Patients	19.6%	90.9%	0.553

- Higher specificity was chosen with maximum AROC

Results

	Sensitivity	Specificity	AROC
Simple model: optimised specificity			
Current CD4, CD4 change over 6 and 12 months			
Patients	22.2%	90.2%	0.562
Simple model: optimised sensitivity			
Current CD4, CD4 change over 6 and 12 months			
Patients	76.9%	33.0%	0.549

- Better specificity and sensitivity could be achieved with the sacrifice of the other
- Overall AROC not satisfactory

Sensitivity analyses

Analysis	WHO criteria (AROC)		Best model (AROC)	
	Observations	Patients	Observations	Patients
Base model	0.609	0.582	0.582	0.580
Viral load <400 c/ml	0.609	0.582	0.632	0.595
Viral load <10 000 c/ml	0.609	0.582	0.644	0.619
Confirmed (repeated) test results	0.602	0.587	0.656	0.648
First line NNRTI regimen	0.610	0.585	0.646	0.621
First virological failure	0.583	0.580	0.718	0.636
Excluding AZT patients	0.613	0.589	0.621	0.608
AHOD only	0.612	0.565	0.639	0.606
TAHOD only	0.597	0.599	0.667	0.636
Excluding TB from clinical criteria	0.609	0.582	-	-
Excluding PTB from clinical criteria	0.609	0.582	-	-
Individuals with regular viral load only	0.608	0.579	0.648	0.621
Sites with regular viral load only	0.611	0.583	0.644	0.616

Summary

- Performance of WHO criteria similar to previous studies and robust across cohort and multiple other sensitivity analyses emphasizing generalisability of findings.
- A comprehensive investigation was not able to identify a superior definition of treatment failure suggesting there are inherent limits to the ability of clinical criteria and CD4 counting to predict virological failure.
- Clinical criteria add little to performance of CD4 criteria.
- Simpler criteria more closely linked to prognosis (current CD4) may be able to be identified.
- Adjustment to cut-points may allow improved sensitivity for use as a screening test in combination with targeted VL.