A predictive risk model for first line treatment failure in South Africa

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INTRODUCTION

Background

Although individual predictors of first line antiretroviral therapy (ART) failure have been identified, few studies in resource-limited settings have been large enough for predictive modeling. Understanding the absolute risk of first line failure is useful for patient monitoring and for effectively targeting limited resources for second line ART.

Objectives

1) To estimate absolute risk of failure of first line ART over 5 years on ART as a function of key demographic, clinical, and immunologic factors at the start of ART

2) To develop a predictive model for other South African clinics to identify patients at high risk of failure.

METHODS

- **Design:** Observational cohort
- **Data:** Medical records from 9 South African public HIV clinics
- **Inclusion:**
  - Patients initiated on first line ART after 2004 with at least 6 months of follow-up time.
- Accelerated failure time models
  Person time
  - Start: 6 months after ART start
  - End: 2 consecutive viral loads >1000 copies/mL

Candidate Predictor Variables

Demographic: Sex, age, history of smoking and alcohol use, pregnancy

Lab values: CD4, hemoglobin, RBC, MCV, AST, ALT, creatinine clearance

Clinical measures: WHO stage, body mass index (BMI), history of TB, peripheral neuropathy

Treatment: ARVs in first line regimen, missed visits in first 6 months on treatment

Model Development

1. Diagnostic plots to choose survival distribution to fit data for accelerated failure time models
2. Unadjusted accelerated failure time models for individual predictors (stratified by clinic)
3. Adjusted accelerated failure time model (stepwise selection of predictors)
4. Impute missing data
5. Re-run adjusted models
6. Cross validation of models w/imputed data
   - ➢ Develop model on all clinics but one
   - ➢ Test model on excluded clinic
   - ➢ Rotate excluded clinic (9 times)
   - ➢ Output weighted average of:
     - **Harrell's C statistic**
       % of patients for whom model correctly discriminates failure
     - **Difference between actual and predicted 5-year failure**

RESULTS

Final Model

- Final Distribution:
  - Weibull
- C-statistic:
  - 60.1%
- Difference between predicted and actual 5 year failure:
  - 0.03%

Accelerated failure time model estimates used to calculate scores for risk groups:

RISK SCORE CALCULATION

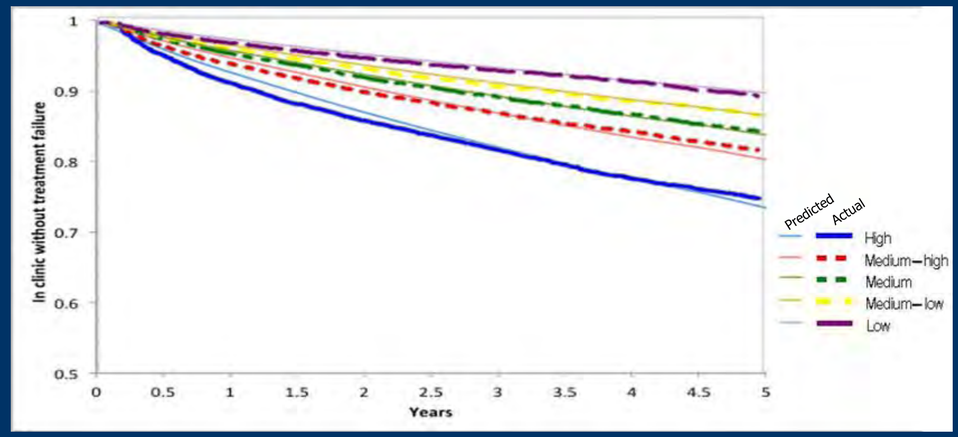
1. Sex & age:			**3. CD4 count:**	0-25	10
Females:	Age:			25-50	8
	18-24.9	8		51-100	6
	25-29.9	6		101-200	4
	30-34.9	4		201-350	2
	35-39.9	2		>350	0
	40-44.9	1			
	45+	0	**4. MCV:**	<80	0
Males:	Age:			80-95	1
	18-24.9	7		95+	3
	25-29.9	6			
	30-34.9	5	**5. Hemoglobin:**	<12	1
	35-49.9	4		12+	0
	50+	3			
			6. History of TB:	Yes	1
2. NNRTI:	NVP	3		No	0
	EFV	0			
			7. Missed visits during first 6 months on treatment:	Yes	4
				No	0

SCORE	RISK GROUP
>17	High
14-17	Medium-high
12-13	Middle
9-11	Medium-low
0-8	Low

Prediction of 5-Year Treatment Failure

	Years on ART:				
Risk group:	1	2	3	4	5
High	3.8%	10.1%	15.4%	20.1%	24.4%
Medium-high	2.7%	7.3%	11.2%	14.7%	18.0%
Medium	2.2%	5.9%	9.1%	12.1%	14.8%
Medium-low	1.8%	4.9%	7.5%	10.0%	12.3%
Low	1.4%	3.7%	5.7%	7.6%	9.4%

Comparison between model-predicted treatment failure and actual failure over time on ART for study population



CONCLUSION

The predictive model was able to discriminate between patients at higher risk of first line virologic failure. 24% of patients at highest risk failed treatment in 5 years. Identification of patients at highest risk of failure is useful for patient monitoring, referral for adherence counseling, and targeting adherence interventions to improve patient outcomes and avoid need for second line ART.

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