A Clinical Prediction Rule for PI resistance in resource limited settings

Abstract 604

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Introduction

Virological failure is common in adults on 2nd line ART in resource limited settings, occurring in up to 38% of patients at 3 years [1]. Most patients failing therapy do not have major protease inhibitor (PI) resistance mutations [2,3,4]. Therefore, empiric switches to salvage therapy would waste resources. Resistance testing identifies patients needing salvage therapy, but is expensive and access is limited. Therefore, a clinical prediction rule (CPR) to rationalise access to resistance testing would be a valuable tool.

Methods

- We included adults from a South African managed-care cohort with virological failure (VL >400 copies/mL on ≥2 occasions) and ≥4 months exposure to ritonavir-boosted atazanavir or lopinavir before genotyping.
- We defined PI resistance as ≥ 1 major mutation/s to current PI.
- We constructed a multivariate logistic regression model to identify predictors of PI resistance. We included the following variables in the model based on an *a priori* decision: age, sex, PI duration, adherence by pharmacy claims, concomitant CYP3A4-inducing drugs and viral load at time of genotyping.
- We selected variables included in the CPR using a stepwise approach.
- We internally validated by bootstrapping.
- We categorised included variables, and assigned points to each level based on the adjusted beta coefficients.

Results

Table 1. Patient characteristics (n=339)

Variable	Category	PI resistance n=146	No PI resistance n=193	p-value
Age				
Median years (IQR)		44 (40 to 48)	39 (35 to 45)	<0.001
Female sex				
n (%)		79 (54)	132 (68)	0.007
CD4 count				
Median cells/μL (IQR)		110 (39 to 205)	136 (42 to 237)	0.328
Viral load				
Median $\log_{10}$ last (IQR)		4.9 (4.2 to 5.4)	4.9 (4.3 to 5.4)	0.712
PI				
n (%)	LPVr	136 (93)	173 (90)	
n (%)	ATVr	10 (7)	20 (10)	0.259
PI duration				
Median years (IQR)		3.3 (1.9 to 5.8)	2.2 (1.4 to 4.0)	<0.001
Adherence				
Median % last 4 months (IQR)		98.3 (90.0 to 100)	93.3 (46.7 to 100)	<0.001
Inducing drugs				
n (%)	Any in past 12 months	12 (8)	19 (10)	0.607

Results (continued)

Table 2. Univariate and multivariate associations with major PI mutations

Variable	Category (n)	Crude OR	Crude 95% CI	Crude Wald test p-value	Adjusted OR	Adjusted 95% CI	Adjusted Wald test p-value
Age [1]		2.08	1.55 to 2.81	<0.001	1.91	1.39 to 2.63	<0.001
Sex	f (211)	*referent*			*referent*		
	m (128)	1.88	1.20 to 2.94	0.006	1.46	0.89 to 2.39	0.135
Viral load [2]		0.99	0.76 to 1.28	0.914	1.16	0.86 to 1.56	0.341
PI duration [3]		1.19	1.08 to 1.30	<0.001	1.15	1.04 to 1.26	0.006
Adherence [4]		1.23	1.13 to 1.34	<0.001	1.22	1.11 to 1.33	<0.001
Inducing drugs							
	no (308)	*referent*			*referent*		
	yes (31)	0.82	0.38 to 1.75	0.608	0.87	0.38 to 2.00	0.740

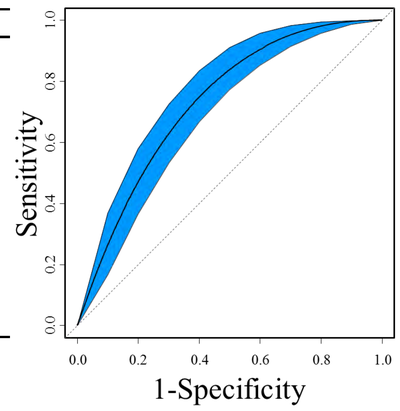
[1] Per 10 year increase in age
[2] Per $\log_{10}$ increase in viral load at time of genotyping
[3] Per 1 year increase in duration
[4] Per 10% increase in adherence over last 4 months

- There was PI resistance in 43% of patients (146/339).
- In the multivariate analysis, major PI resistance mutations were associated with increasing age, longer PI exposure and higher adherence (Table 2).
- We therefore included age, PI duration and adherence in the CPR.

Table 3. Major PI mutations detected (146 patients with ≥ 1 mutation)

Major PI Mutations	n (%)
32I	7 (2)
33F	29 (9)
46IL	102 (30)
47VA	14 (4)
48VM	9 (3)
50V	7 (2)
54VTALM	105 (31)
76V	42 (12)
82AFTS	105 (31)
84V	27 (8)
90M	21 (6)

Figure 1. ROC curve for the prediction of major PI mutations



Results (continued)

- Area under the ROC curve was 0.736 (95% CI 0.683 to 0.789) before and 0.739 (95% CI 0.736 to 0.742) after bootstrapping (Figure 1).
- The model had acceptable calibration.
- Scoring of the CPR is detailed in Table 4 below.
- The optimal cut point corresponded to a score of 8/15 (75% sensitivity and 67% specificity).

Table 4. Clinical prediction rule for major PI resistance mutations

Risk factor	Points assigned
Age (years)	
18-29	0
30-39	2
40-49	4
50-59	6
60-65	8
Duration on PI (years)	
<2 years	0
2-4 years	1
5-11 years	3
Adherence last 4 months	
0-39%	0
40-59%	2
60-79%	3
80-100%	4

Score	Predicted probability	Sensitivity	Specificity
0-2	≤8.6%	100%	≤2%
3	11.8%	99%	8%
4	15.8%	99%	12%
5	20.9%	98%	19%
6	27.2%	94%	31%
7	34.5%	82%	48%
8	42.6%	75%	67%
9	51.1%	60%	75%
10	59.6%	38%	85%
11	67.5%	32%	90%
12	74.6%	5%	98%
13	80.5%	5%	98%
14-15	≥85.4%	≤1%	100%

Discussion

We found that PI resistance was present in 43% of patients. This is higher than previously described in South Africa [2,3,4] possibly due to the long duration of PI exposure in this cohort. Older patients with high adherence and prolonged PI exposure are most likely to benefit from resistance testing to guide selection of a 3rd line ART regimen. The CPR may be a useful tool to rationalise patient selection for resistance testing in resource limited settings, but requires external validation.

References

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