THE PROGNOSTIC VALUE TO PREDICT VIROLOGICAL OUTCOMES OF 14 DISTINCT SYSTEMS USED TO INTERPRET THE RESULTS OF GENOTYPIC HIV-1 DRUG RESISTANCE TESTING IN UNTREATED PATIENTS STARTING THEIR FIRST HAART

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BACKGROUND

Several interpretation systems (IS) can be usefully employed to encode HIV-1 genotypic resistance and guide rescue therapy after failure

Role of existing IS in predicting virological outcomes based on genotypes from individuals not exposed to therapy has yet to be determined

METHODS-1

Baseline isolates from antiretroviral-naive patients of ICONA initiating the first HAART were retrospectively genotyped (ABI)

Definition of virological success: time to the first VL≤500 copies/ml

Definiton of virological failure: time to the first of two consecutive VL>500 copies/ml after week 24

METHODS-2

Analyses performed by ignoring tretment chenges (ITC): any change in tretment was ignored and follow-up was right truncated at the time of the last viral load

Genotypes were interpreted using 14 IS including 10 rule-based algorithms, 1mutations table and 3 genotype-phenotype correlation systems

CHARACTERISTIC OF PATIENTS-1

417 patients (77,2% M); Geno2pheno scores were available for a subset of 332 individuals

Median Age: 36 Y (IQR 32-41)

HIV risk factor:	
heterosexual	33%
MSM	26%
IDU	34%
other/unknown	8%

CHARACTERISTIC OF THE PATIENTS-2

Previous AIDS: 19,2%

Median CD4+: 263 cells/µl (IQR 78-449)

Median HIV RNA: 4.91 $\log_{10}$ c/ml (IQR 4,50-5,40)

ANALYSED INTERPRETATION SYSTEMS

1) Stanford hivdb algorithm.
2) Trugene (Visible Genetics) GuideLines 5.0algorithm.
3) ANRS-AC11 algorithm (v06/2002)
4) KU Leuven Rega 5.5 algorithm.
5) Vertribrae HIV resistanceWeb table.
6) Menéndez-Arias algorithm (2002).
7) Retrogram 1.6 algorithm.
8) RCG algorithm.
9) Detroit Medical Center algorithm.
10) University Sao Paulo, Brazil,algorithm.
11) CHL v4.0 Luxemburg algorithm.
13) Geno2pheno 2.1 software decision tree
14) Geno2pheno 2.1 software support vector machines (SVM)
15) Geno2pheno 2.1 software predicted fold-resistance (SVM regression) based on default cutoffs

SCORING SYSTEMS

System	Susceptibility score 0	0.33	0.5	0.66	1
Stanford hivdb	Intermediate/high level resistance		Low level resistance		Susceptible; potential low level resistance
Trugene 5.0	Resistance		Possible resistance		No evidence of resistance
ANRS-AC11	Resistance		Possible resistance		No evidence of resistance
Rega 5.5	Resistance		Possible resistance		No evidence of resistance
Vertribrae hivresistanceWeb	Resistance mutations		Mutations that "contribute to resistance"		No resistance or accessory mutations
Menéndez-Arias	Resistance				Susceptible
Retrogram 1. 6	Ranking level D	Ranking C		Ranking B	Ranking A
RCG	Resistance			D4T, DDI, DDC (0.75) with specific mutations	Susceptible
Detroit	Resistance		Possible resistance		No evidence of resistance
Sao Paulo	Resistance		Possible resistance		No evidence of resistance
CHL v4.0 Luxemburg	Resistance		Possible resistance		No evidence of resistance
Geno2pheno decision tree	Resistance				No evidence of resistance
Geno2pheno SVM	Resistance				No evidence of resistance
Geno2pheno SVM regression	Resistance				No evidence of resistance

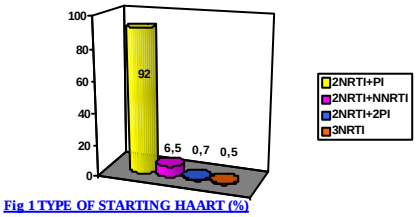


Fig 1 TYPE OF STARTING HAART (%)

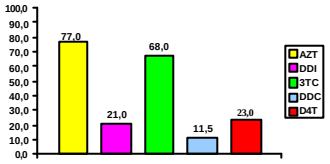


Fig 2 NRTI included in the 1st HAART

1) Prevalence of patients with PR mutations before starting HAART

		N	% of patients
Number of total PR mutations			
None		182	43.6
1		189	45.3
2		39	9.4
3		6	1.4
5		1	0.2
No. with major PR mutations			
None		413	99.0
1		4	1.0
No. with minor PR mutations			
None		183	43.9
1		190	45.6
2		37	8.9
3		6	1.4
4		1	0.2

2) Prevalence of patients with RT mutations before starting HAART

		N	% of patients
Patients with mutations			
RT	PR		
no	no	164	39.3
yes	no	18	4.3
no	yes	214	51.3
yes	yes	21	5.0
Number with RT mutation			
None		378	90.6
1		32	7.7
2		6	1.4
3		1	0.2
Number with NAMS			
None		378	90.6
1		32	7.7
2		6	1.4
3		1	0.2
No. with NNRTI mutations			
None		414	99.3
1		1	0.7

3) Relative hazards of virological success (<500 copies/ml) from fitting a Cox regression model-analysis by ignoring treatment changes (ITC)

(All RHs are for 1 unit higher of the GSS)

	Crude analysis		*Adjusted analysis	
System	RH (95% CI)	p-value	RH (95% CI)	p-value
VG	2.33 (0.83-6.58)	0.11	2.42 (0.88-6.64)	0.09
Retrogram 1.6	1.78 (0.59-5.40)	0.31	1.89 (0.64-5.60)	0.25
Vertibrae (V.3)	1.82 (1.07-3.10)	0.03	1.81 (1.06-3.12)	0.03
Menéndez 2002	1.73 (0.87-3.44)	0.12	1.82 (0.92-3.61)	0.09
RCG	1.57 (0.87-2.82)	0.14	1.56 (0.86-2.84)	0.15
Stanford dbase	1.73 (0.91-3.27)	0.09	1.75 (0.91-3.35)	0.09
ANRS-AC11 (06-2002)	1.63 (0.93-2.88)	0.09	1.76 (1.00-3.17)	0.05
Rega 5.5	1.68 (1.12-2.51)	0.01	1.83 (1.21-2.77)	0.004
Detroit	1.41 (0.84-237)	0.20	1.55 (0.91-2.64)	0.11
Sao Paulo	1.34 (0.85-2.09)	0.20	1.40 (0.89-2.20)	0.15
Luxembourg Abl 4.0	2.11 (1.00-4.84)	0.05	2.12 (1.01-4.47)	0.05
DTS n=332	1.80 (0.99-3.29)	0.06	1.89 (1.03-3.44)	0.04
SVM n=332	1.21 (0.77-1.91)	0.41	1.34 (0.84-2.16)	0.22
SVMRG n=332	1.11 (0.77-1.61)	0.57	1.10 (0.75-1.61)	0.62

4) Results from hierachical linear model ITC

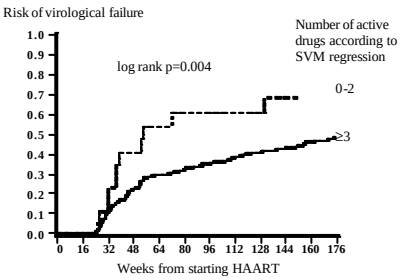
(Mean VL changes for 1 unit higher of the GSS)

	Crude analysis		Adjusted analysis	
System	MEAN LOG10 change VL	p-value	MEAN LOG10 change VL	p-value
GuideLines 5.0	-0.026	0.85	-0.02	0.95
Retrogram 1.6	-0.02	0.92	-0.02	0.86
HivresistanceWeb 3	-0.18	0.20	-0.14	0.31
Menéndez-Arias 2002	-0.18	0.26	-0.15	0.32
RCG	-0.03	0.82	-0.005	0.97
Stanford dbase	-0.06	0.73	-0.02	0.91
ANRS-AC11 v 06/02	-0.27	0.05	-0.25	0.05
Rega-Institute v 5.5	-0.24	0.03	-0.26	0.01
Detroit	-0.03	0.86	-0.10	0.46
Sao Paulo	-0.21	0.09	-0.20	0.10
Luxembourg v 4.0	+0.07	0.70	+0.12	0.51
DT n=332	-0.12	0.46	-0.13	0.42
SVM n=332	-0.19	0.07	-0.26	0.01
SVMRG n=332	-013	0.15	-0.18	0.05

5) Relative hazards of virological failure from fitting a Cox regression model-analysis by ITC

(All RHs are for 1 unit higher of the GSS)

	Crude analysis		Adjusted analysis	
System	RH (95%CI)	p-value	RH (95% CI)	p-value
VG	1.19 (0.32-4.50)	080	1.23 (0.29-5.10)	0.78
Retrogram	1.09 (0.39-3.00)	087	1.24 (0.44-3.53)	0.68
Vertibrae	0.75 (0.46-1.21)	023	0.82 (0.50-1.33)	0.42
Menéndez-Arias	0.88 (0.51-1.53)	065	0.98 (0.55-1.72)	0.93
De Gruttola	0.96 (0.55-1.67)	087	1.00 (0.58-1.74)	0.99
Stanford dbase	0.66 (0.36-1.19)	017	0.73 (0.40-1.34)	0.31
ANRS-AC11	0.79 (0.49-1.27)	033	0.85 (0.53-1.36)	0.49
Rega-Institute	0.74 (0.48-1.13)	016	0.74 (0.49-1.12)	0.15
Detroit	0.88 (0.52-1.51)	065	0.85 (0.51-1.42)	0.54
Sao Paulo	0.77 (0.49-1.20)	024	0.86 (0.54-1.36)	0.51
Luxembourg	1.05 (0.44-2.49)	091	1.35 (0.55-3.22)	0.52
DT n=332	0.72 (0.34-1.55)	040	0.74 (0.34-1.62)	0.45
SVM n=332	0.80 (0.49-1.30)	037	0.74 (0.45-1.22)	0.23
SVMRG n=332	0.71 (0.49-1.04)	007	0.64 (0.43-0.96)	0.03



CONCLUSIONS

- IS can usefully predict virological outcomes of HAART in previously naive patients from pre-therapy resistance genotypes
- A system calculating quantitative phenotypic susceptibilit y from genotypes was the best at predicting virological failure after 24 wks of treatment
- Despite the low prevalence of primary resistance mutations (9.4% for NRTI, ≤1% for NNRTI and PI), genotyping coupled with adequate interpretation in chronic naive patients could usefully predict subsequent treatment outcomes