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Performance of genotypic algorithms for predicting tropism for HIV-1 CRF01_AE recombinant

C. Soulie^{a,b,*}, L. Morand-Joubert^{a,c}, J. Cottalorda^d, C. Charpentier^e, P. Bellecave^f, L. Le Guen^g, S. Yerly^h, B. Montesⁱ, S. Fafi-Kremer^j, J. Dina^k, V. Avettand-Fenoel^{l,m}, C. Amielⁿ, C. Roussel^o,

C. Pallier^p, K. Zafilaza^{a,b}, S. Sayon^{a,b}, A. Signori-Schmuck^q, A. Mirand^r, M.A. Trabaud^s, S. Berger^t, V. Calvez^{a,b}, A.G. Marcelin^{a,b}, on behalf of the ANRS AC11 resistance group

^a Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), Paris, France ^b AP-HP, Hôpital Pitié-Salpêtrière, Service de Virologie, Paris, France ^c AP-HP, Hôpital Saint Antoine, Service de Virologie, Paris, France ^d Laboratoire de Virologie, CHU, Nice, France ^e IAME, UMR 1137-Université Paris Diderot, Sorbonne Paris Cité, INSERM, AP-HP, Hôpital Bichat, Laboratoire de Virologie, Paris, France ^f CHU de Bordeaux, Laboratoire de Virologie, Univ. Bordeaux, CNRS UMR 5234, Bordeaux, France ^g Laboratoire de virologie, CHU, Nantes, France ^h Laboratory of Virology, Geneva University Hospitals, Switzerland ⁱ Laboratoire de Virologie, CHU, Montpellier, France ^j Laboratoire de Virologie, CHU, Strasbourg, France ^k Laboratoire de virologie, CHU, Caen, France ^l AP-HP, Laboratoire de Virologie, Hôpital Necker, Paris, France ^m Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, EA7327, France ⁿ AP-HP, Laboratoire de Virologie, Hôpital Tenon, Paris, France ^o CHU, Amiens, France ^p CHU Bicêtre, Paris, France ^q CHU, Grenoble, France ^r CHU, Clermont-Ferrand, France ^s Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France

^t Laboratoire de Virologie, CHU de Nancy Brabois, EA 7300, Université de Lorraine, Faculté de Médecine, Vandoeuvre les Nancy, France

Objectives: There is no consensus about the performances of genotypic rules for predicting HIV-1 non-B subtype tropism. Three genotypic methods were compared for CRF01_AE HIV-1 tropism determination.

Methods: The V3 env region of 207 HIV-1 CRF01_AE and 178 B subtypes from 17 centers in France and 1 center in Switzerland was sequenced. Tropism was determined by Geno2Pheno algorithm with false positive rate (FPR) 5% or 10%, the 11/25 rule or the combined criteria of the 11/25, net charge rule and NXT/S mutations.

Results: Overall, 72.5%, 59.4%, 86.0%, 90.8% of the 207 HIV-1 CRF01_AE were R5-tropic viruses determined by Geno2pheno FPR5%, Geno2pheno FPR10%, the combined criteria and the 11/25 rule, respectively. A concordance of 82.6% was observed between Geno2pheno FPR5% and the combined criteria for CRF01_AE. The results were nearly similar for the comparison between Geno2pheno FPR5% and the 11/25 rule. More mismatches were observed when Geno2pheno was used with the FPR10%. Neither HIV viral load, nor current or nadir CD4 was associated with the discordance rate between the different algorithms.

Conclusion: Geno2pheno predicted more X4-tropic viruses for this set of CRF01_AE sequences than the combined criteria or the 11/25 rule alone. For a conservative approach, Geno2pheno FPR5% seems to be a good compromise to predict CRF01_AE tropism.

Keywords: HIV, tropism, CRF01_AE, Genotypic prediction

Background

The chemokine receptors CCR5 and CXCR4 are the principal coreceptors for entry of HIV-1 into target cells [1,2]. Co-receptor selectivity is determined by genetic sequences within HIV glycoprotein 120 (gp120), particularly in a highly variable and structurally flexible region termed 'V3' which is involved in co-receptor binding [3–5]. The CCR5 antagonists, which inhibit HIV-1 binding on the CCR5-coreceptor, are only active on R5-tropic viruses which implies a tropism determination before their prescription. Then, the determination of tropism is useful in clinical practice.

The simplest genotypic rules such as the 11/25 rule, predict X4 on the basis of the presence of basic residues 11 or 25 of the HIV gp120 V3 loop. The combined criteria of the 11/25, net charge rules and the presence of specific determinants in the gp120 V3 loop were also used to determine HIV tropism [6]. Now, several bioinformatics methods for prediction of HIV coreceptor usage have been proposed, are available as online tools and the most used of them is Geno2pheno [coreceptor] [7]. However, Geno2pheno is based on HIV B subtype V3-loop as viral sequence information input.

The HIV-1 CRF01_AE recombinant is dominant in Asia where its prevalence is 84%, and has contributed towards 4.6% of total HIV-1 infections in terms of worldwide distributions [8,9]. In some European countries, the CRF01_AE was the second major recombinant among HIV non-B subtypes after the CRF02_AG recombinant [10,11]. Several studies underlined the high prevalence of X4-tropism for CRF01_AE recombinant associated with a possible fast disease progression [12–14].

The genotypic determination is now commonly used to determine tropism for HIV-1 B subtype. Because of the increase of HIV non-B subtypes prevalence, the possibility of fast disease progression for the CRF01_AE recombinant and the debate on the performances of genotypic rules or algorithms, it is important to evaluate the performance of different rules or algorithms to determine HIV tropism.

Objectives

The aim of this study was to compare 3 genotypic methods on a set of 207 HIV-1 CRF01_AE recombinants to evaluate the concordance between these measures of HIV-1 tropism.

Study design

This study has enrolled 207 HIV-1 patients infected by CRF01_AE recombinant from 17 centers in France and 1 center in Switzerland. For the comparison of sequences, 178 HIV-1 patients infected by B subtype were studied. The V3 env region was sequenced as previously described and tropism was determined by Geno2pheno algorithm (False Positive Rate, FPR5% or FPR10%, <http://coreceptor.bioinf.mpi-inf.mpg.de/>), the 11/25 rule or the combined criteria of the 11/25, net charge rule and NXT/S [6,15]. Comparisons between groups were performed using Statview Software with the non-parametric Mann-Whitney or chisquared tests.

Results

The CRF01_AE HIV-1 patients had a median plasma HIV-1 viral load of 4.32 log copies/mL (range 1.30-6.79), a median CD4 cell count of 373 cells/mm³ (range 2–1954) and a median of nadir CD4 cell count of 237 cells/mm³ (range 2–993).

A consensus sequence was established with the main amino acid at each of the 35 positions of the V3 loop for B subtypes and CRF01_AE subtypes (Table 1A). At key position 25, R was statistically less frequent for the CRF01_AE recombinant (p = 0.0289) (Table 1B).

Overall, 72.5%, 59.4%, 86.0%, 90.8% of the 207 HIV-1 CRF01_AE were R5-tropic viruses determined by Geno2pheno FPR5%, Geno2pheno FPR10%, the combined criteria and the 11/25 rule, respectively. A concordance of 82.6% (71.0% R5 and 11.6% X4) was observed between Geno2pheno FPR5% and the combined criteria for CRF01_AE (Fig. 1). The results were nearly similar for the comparison between Geno2pheno FPR5% and the 11/25 rule. More mismatches were observed when Geno2pheno was used with the FPR10% (Fig. 1).

Neither HIV viral load, nor current or nadir CD4 was associated with the discordance rate between the different algorithms.

Discussion

The HIV tropism determination was different according to the algorithm used (Geno2pheno FPR5%, Geno2pheno FPR10%, 11/25 rule, and 11/25 rule combined to net charge rule and NXT/S mutation) for this set of CRF01_AE recombinant sequences. The Geno2pheno algorithm predicted more X4-tropic viruses than the two other manual rules. Then, Geno2pheno seems to be more careful concerning the prediction of tropism in regards to the prescription of CCR5 antagonists.

The Geno2pheno algorithm was built on phenotypic-genotypic correlation using HIV-1 B subtype samples [7]. HIV genetic variability between B subtype and CRF01_AE recombinant, especially for the gp120 V3 region, can have consequently an impact on the tropism determination by genotypic algorithms [6,15–17]. Regarding the potential impact of the subtype on the CCR5 inhibitor maraviroc activity, it is important to have cautious rules to determine the HIV tropism to allow adequate prescription of this inhibitor [18–20].

We previously demonstrated that the Geno2pheno FPR5% could be used to predict tropism as well as other genotypic rules for the HIV-1 CRF02_AG recombinant [21]. The present study shows that, for a conservative approach, Geno2pheno FPR5% seemed to be also a good compromise to predict CRF01_AE tropism. The use of this algorithm could facilitate the prediction of HIV tropism in clinical practice.

gp120	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330
V3loop	I	2	S	4	S	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
B	C	T	R	P	N	N	N	T	R	K	S	I	R	I	Q	R	G	P	G	R	A	F	V	T	I	Q	I	G	D	M	R	Q	A	H	C
CRF01_AE	C	T	R	P	N	N	T	R	K	S	I	R	I	Q	R	G	P	G	R	A	F	V	T	I	Q	I	G	D	M	R	Q	A	H	C	
p	0.9999	0.1169	0.9999	0.9999	0.0001	0.1365	0.9999	0.9498	0.5141	0.0001	0.0001	0.0001	0.0001	0.0002	0.0001	0.8104	0.4378	0.0001	0.0182	0.0011	0.0073	0.0001	0.5882	0.0007	0.0001	0.0422	0.9999	0.2309	0.0388	0.0302	0.0378	0.0002	0.3031	0.0001	0.1608

Conflicts of interest statement None to declare.

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Amino acid consensus sequences of V3 loop-gp120 HIV B subtype and CRF01_AE recombinants.

Gp120	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330
V3loop	T	Z	S	I	S	G	T	S	S	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
HXB2	G	T	R	P	N	N	T	R	K	S	I	R	I	Q	R	Q	P	G	R	A	F	V	T	I	G	I	Q	D	M	R	Q	A	H	G	
B	C	T	S	F	N	N	T	R	Q	S	I	R	I	G	P	G	R	A	F	V	A	V	G	D	I	I	D	D	I	R	Q	A	H	G	
CRF01_AE	C	T	S	F	N	N	T	R	T	D	I	R	I	G	P	G	Q	V	F	V	R	T	G	D	I	I	D	D	I	R	K	A	V	C	
p	0.9999	0.1189	0.9999	0.9999	0.0001	0.1865	0.9999	0.0496	0.5141	0.0001	0.0001	0.0001	0.0001	0.0002	0.0001	0.8104	0.4338	0.0001	0.0162	0.0011	0.0073	0.0001	0.5802	0.0007	0.0001	0.0422	0.9999	0.2269	0.0288	0.6302	0.6378	0.0002	0.0031	0.0001	0.1600

Table 1B

Distribution of amino acid at position 11 and 25 of V3 loop-gp120. In bold, the major amino acid.

		B subtype	CRF01_AE recombinant
11 S	A	0.5	
	D	1.5	
	G	29.0	13.2
	H		0.5
	K		1.0
	L	0.5	
	N	0.5	1.0
	P		0.5
	R	7.5	8.5
	S	59.5	75.4
25 I	T	0.5	0.5
	Y	0.5	
	A	5.7	6.4
	D	33.0	56.1
	E	22.2	17.0
	G	5.7	8.5
	H	1.4	0.9
	I	7.1	2.6
	K	2.4	1.3
	N	3.8	3.4
Q	9.4	1.7	
R	6.1	0.4	
S	2.8	0.9	
T	0.5	0.4	
V		0.4	

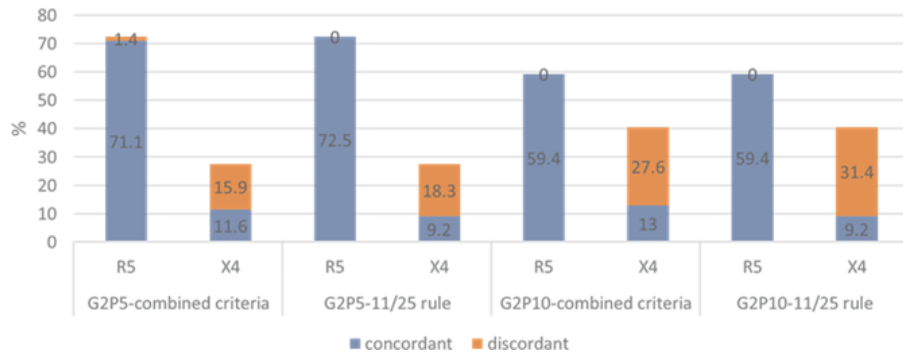


Fig. 1. Representation of tropism prediction by different algorithm for CRF01_AE recombinant.