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HIV-1 group O phenotypic susceptibility to integrase inhibitors

Anne Tourneroche[1], Elodie Alessandri-Gradt[1,2], Gilles Collin[3], Marie Leoz[1,2], Charlotte Charpentier[3,4], Diane Descamps[3,4] and Jean-Christophe Plantier[1,2]

[1] GRAM EA2656, UFR Médecine-Pharmacie, Université de Normandie, France ; [2]Laboratoire de virologie associé au CNR du VIH, CHU Charles Nicolle, Rouen, France ; [3]Laboratoire de virologie, Groupe hospitalier Bichat-Claude Bernard, AP-HP, France ; [4]EA4409, PRES, Université Paris Diderot, Sorbonne Paris Cité, France

Introduction

HIV-1 genetic diversity leads to a classification into 4 groups : group M, responsible for the pandemic situation, group O (HIV-1/O) endemic in Cameroon , group N and P more rare.

It has been showed that HIV-1/O has a natural high genetic polymorphism that may have serious outcomes on antiretroviral treatment response [1]. The more recent drugs, such as integrase inhibitors (II) including Raltegravir (RAL), Elvitegravir (EVG) and Dolutegravir (DTG), could be a reliable alternative for therapy management in patients infected with these viruses. Yet few data are available regarding the susceptibility of these viruses to II and only refer to clinical case report or some *in vitro* studies on restricted numbers of strains.

Objectives

Given :

- the natural genetic polymorphism of HIV-1/O
- limited data on II efficacy *in vivo* and *in vitro*,

we aimed to **determine the natural susceptibility of HIV-1/O clinical isolates to RAL, EVG and DTG in a phenotypic assay** by measuring the concentration of drugs that inhibits 50% of viral inocula (IC_{50}).

Material & Methods

Thirteen clinical isolates representative of the intra-group O genetic diversity (7 clade A, 3 clade B, 1 clade C, 2 divergent) and 1 lab reference strain of HIV-1/M (BRU, susceptible to II) were studied.

A 3 days-long phenotypic assay was carried out by expanding each isolate on peripheral blood mononuclear cells from healthy donors, in presence of increasing concentrations of II ranging from 0 nm to 2 000 nm *(Fig1).* Replication was measured by viral load using a specific HIV-1/O qRT-PCR [2]. IC_{50} values were calculating from the linear equation between the viral load diminution and the increasing concentrations of drugs. The assay was standardized on each strain growth during the test and the incubation time was adjusted if necessary to 2 days or 4 days.

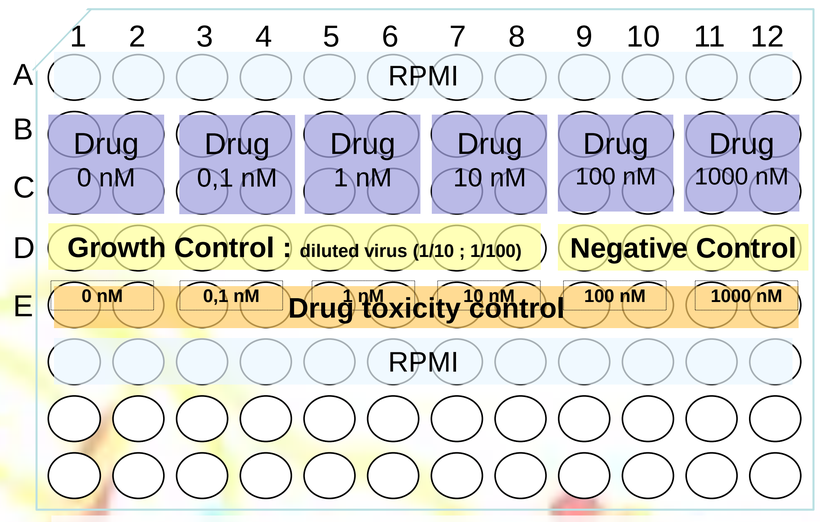

Fig.1 : Phenotypic assay technical conditions

B,C: 100 µl of cell suspension at 2.10^6 cells/ml previously infected with viral supernatant added with 100µL of drug solutions
D : 100 µL of cell suspension at 2.10^6 cellules/ml previously infected with diluted viral supernatant (1/10 or 1/100)
«**Negative control**» : 100µL cell suspension at 2.10^6 cells/mL added with 100 µL of media
E : « drug toxicity control » : 100µL cell suspension at 2.10^6cells/mL added with 100µL of drug solutions

Table 1 : IC_{50} results for the 3 drugs DTG, RAL and EVG

		IC_{50} (nM)		
		DTG	**RAL**	**EVG**
BCF001	A	**0,427**	*	**0,01**
BCF111	A	*	**2,83**	*
BCF008	A	*	**0,024**	*
BCF113	A	**0,170**	**0,010**	**2,88**
BCF101	A	**2,65**	**2,74**	*
BCF112	A	*	*	**0,043**
YBF18	A	**0,081**	**0,3228**	*
MVP5180	B	**0,18**	**0,65**	**0,20**
BCF006	B	**1,88**	**0,742**	*
BCF057	B	**0,253**	**3,22**	*
BCF010	C	**0,11**	**3,07**	*
BCF011	DIV	**0,0581**	**0,664**	**0,66**
BCF005	DIV	**3,30**	**2,45**	**0,94**
BRU	HIV-1/M	**2,09**	**2,07**	*
BRU litterature values		***1,86***[3]	***2,17***[3]	***0,4***[4]
IC50 mean values		**0,91**	**1,44**	**3,97**

** technical adjustment required*
Underlined values : IC_{50} higher than for BRU strain

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Results *(table 1)*

Conditions of standardization were more difficult to obtain for EVG and technical adjustments are required to analyze data.

BRU IC_{50} obtained for DTG and RAL were similar to that reported in previous studies leading to the validation of our results.

DTG IC_{50} obtained for 10 isolates ranged from $5,81.10^{-3}$nM to 3,30nM with a mean value at 0,911nM, and was 2,09nM for BRU. IC_{50} for RAL were scattered over a range extending from $1,0.10^{-2}$nM to 3,22nM (N=11), the mean was 1,44nM and IC_{50} for BRU was 2,07nM. Preliminary results for EVG on 6 isolates showed a mean IC_{50} of 3,97nM. The large majority of HIV-1/O IC_{50} were lower than BRU IC_{50}, but a few strains have higher IC_{50} (DTG : N=2 ; RAL : N=5) always under a fold change of 2.

Discussion / Conclusion

Natural susceptibility to DTG and RAL for HIV-1/O does not differ from HIV-1/M, as IC_{50} averages are not higher than HIV-1/M IC_{50} (BRU). Further investigations are in progress to complete these preliminary results. Phenotypic results have to be compared to nucleotidic sequence of each isolate to determine if the IC_{50} ranges are linked to a specific natural polymorphism of the HIV-1/O integrase gene.

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