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HIV-1 group O phenotypic susceptibility to integrase inhibitors

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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.

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]. IC₅₀ 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.

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 (IC₅₀).

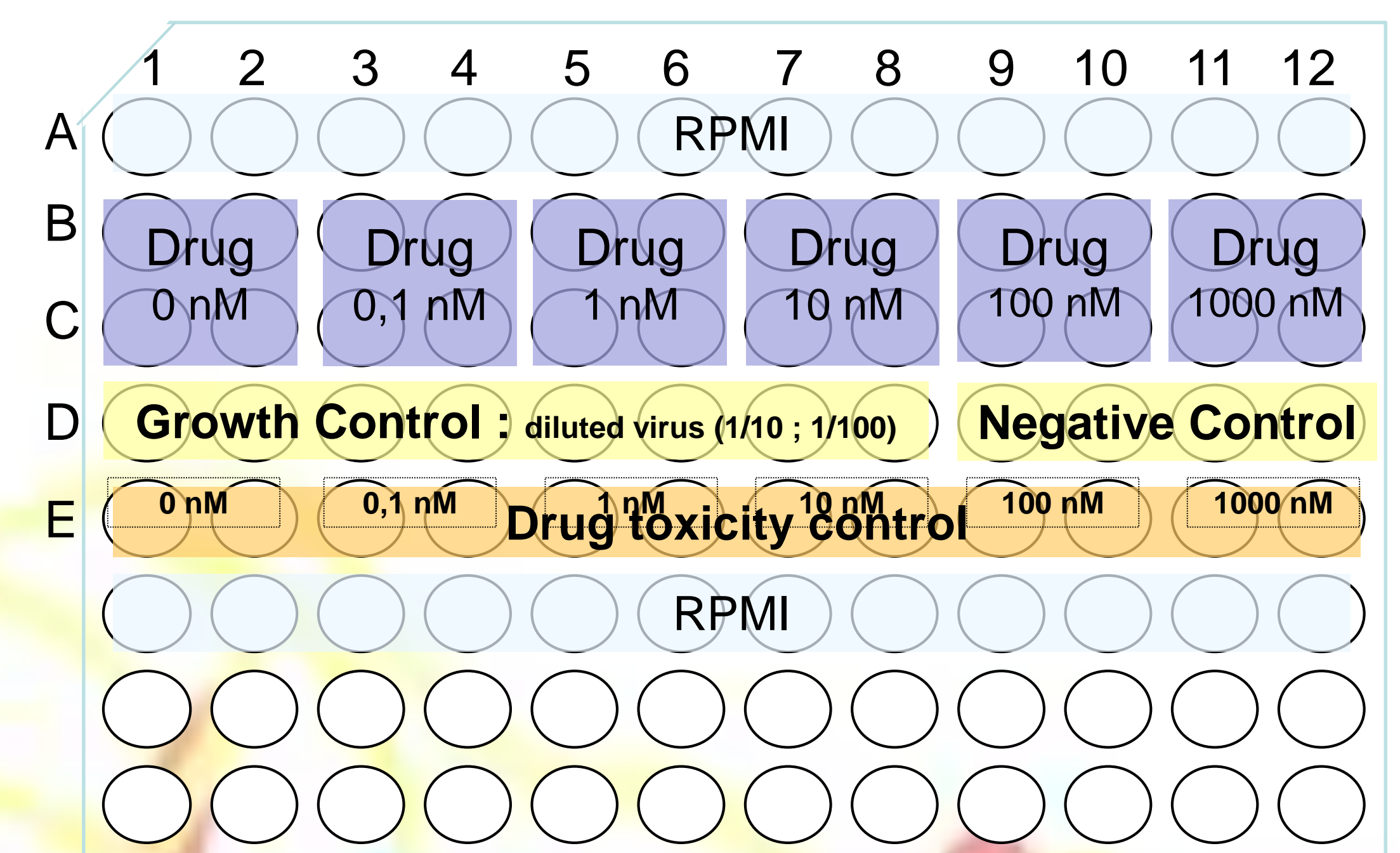


Fig.1 : Phenotypic assay technical conditions

B,C: 100 µl of cell suspension at 2.10⁶ cells/ml previously infected with viral supernatant added with 100µL of drug solutions
D : 100 µL of cell suspension at 2.10⁶ cellules/ml previously infected with diluted viral supernatant (1/10 or 1/100)
«Negative control» : 100µL cell suspension at 2.10⁶ cells/mL added with 100 µL of media
E : « **drug toxicity control** » : 100µL cell suspension at 2.10⁶cells/mL added with 100µL of drug solutions

Table 1 : IC₅₀ 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 : IC₅₀ 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 IC₅₀ obtained for DTG and RAL were similar to that reported in previous studies leading to the validation of our results.

DTG IC₅₀ obtained for 10 isolates ranged from 5,81.10⁻³nM to 3,30nM with a mean value at 0,911nM, and was 2,09nM for BRU. IC₅₀ for RAL were scattered over a range extending from 1,0.10⁻²nM to 3,22nM (N=11), the mean was 1,44nM and IC₅₀ for BRU was 2,07nM. Preliminary results for EVG on 6 isolates showed a mean IC₅₀ of 3,97nM. The large majority of HIV-1/O IC₅₀ were lower than BRU IC₅₀, but a few strains have higher IC₅₀ (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 IC₅₀ averages are not higher than HIV-1/M IC₅₀ (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 IC₅₀ ranges are linked to a specific natural polymorphism of the HIV-1/O integrase gene.

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