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Phenotypic resistance to tenofovir of a multinucleoside resistant HIV-1 strain containing Q151M in association with other specific mutations

Kristel Van Laethem , Myriam Witvrouw, Christophe Pannecouque, Barbara Van Remoortel, Jan Balzarini, Eric De Clercq and Anne-Mieke Vandamme

Rega Institute for Medical Research and University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium

Introduction:

The multinucleoside resistance pattern, characterized by the presence of the Q151M mutation and other mutations in the HIV-1 reverse transcriptase, confers high-level resistance towards most used nucleoside reverse transcriptase inhibitors. Tenofovir is unique that it retains activity against HIV-1 strains displaying this set of mutations. Here, we report a multinucleoside resistant HIV-1 strain that displayed phenotypic resistance towards tenofovir and nucleoside reverse transcriptase inhibitors, which was enhanced upon *in vitro* selective pressure with tenofovir.

Methods:

In vitro selection procedures were performed in the absence of any drug and in the presence of increasing concentrations of tenofovir. The genotypic and phenotypic profiles of the obtained HIV-1 isolates were evaluated.

Results and conclusions:

The multinucleoside resistant HIV-1 strain L6 (S68G, V75I, F77L, F116Y and Q151M) carrying also the lamivudine mutation M184V and the NNRTI mutation K103N, was originally susceptible to tenofovir. However, in the control experiment after in vitro culturing in the absence of tenofovir (L6S), the virus acquired some phenotypic resistance towards tenofovir, associated with the acquisition of the K70T mutation and the loss of the M184 mutation. In the experiment using tenofovir selective pressure (L6/PMPA), the phenotypipc resistance levels towards tenofovir and nucleoside reverse transcriptase inhibitors were further enhanced by the development of the K65R mutation.

Table:

Phenotypic susceptibility (EC_{50} in µM) to a panel of drugs of the different virus strains

		L6	HIV-1 III_B	L6S		L6/PMPA	
	Drug	fold	EC_{50}	EC_{50}	fold	EC_{50}	fold
Nucleoside RT Inhibitors	Zidovudine	**4675**	0.0090 ± 0.0105	**7.5 ± 6**	**833**	**> 468**	**> 52000**
	Zalcitabine	**17**	0.29 ± 0.17	**13 ± 6**	**45**	**23 ± 2**	**79**
	Didanosine	**27**	4.8 ± 0.7	**> 530**	**> 111**	**> 530**	**> 110**
	Stavudine	**71**	0.074 ± 0.028	**1.5 ± 0.1**	**20**	**9.8 ± 0.6**	**132**
	Lamivudine	**25**	0.83 ± 0.68	*12 ± 10*	*14*	**> 546**	**> 658**
	Abacavir	nd	2.6 ± 0.7	**34 ± 19**	**13**	**> 318**	**> 122**
Nonnucleoside RT Inhibitors	Nevirapine	**253**	0.027 ± 0.013	**> 7.5**	**> 278**	**15**	**556**
	Delavirdine	**435**	0.049 ± 0.024	**> 5.7**	**> 116**	**> 5.7**	**> 116**
Acyclic Nucleoside Phosphonates	Tenofovir	1.0	4.2 ± 1.6	**43 ± 14**	**10**	**234 ± 27**	**56**

The results are the average ± SD of 2-8 experiments performed in triplicate. Fold resistance is expressed in comparison to HIV-1 III_B, susceptible values in normal type (< 4-fold resistance), high-level resistance in bold type (> 7-fold resistance towards abacavir, didanosine, stavudine, zalcitabine and tenofovir; > 15- fold resistance towards zidovudine; > 20-fold resistance towards lamivudine, nevirapine and delavirdine) and intermediate values (between susceptible and high-level resistance) in italic type. Fold resistance values for L6 are for purposes of comparison and were obtained in previous experiments. Nd = not determined.