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Phenotypic Impact on Etravirine Susceptibility of Distinct Resistance Mutations in HIV Patients with Prior Failure to Non-Nucleoside Analogues

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BACKGROUND

- Etravirine, formely TMC-125, is the latest approved nonnucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV infection. It exhibits activity against many HIV-1 variants resistant to first-generation NNRTI, such as efavirenz or nevirapine.

- 14 mutations have been associated with a reduced virological response to etravirine: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, and G190S (IAS-USA list, spring 2008).

- The presence of ≥ 3 etravirine resistance-associated mutations (RAMs) is required to substantially impair the virological response to the drug. The only exception seems to be for the presence of Y181C, which with one additional mutation seems to be enough to compromise etravirine activity.

OBJECTIVE

The aim of this study was to assess the phenotypic impact on etravirine susceptibility of specific patterns of resistance mutations in HIV patients with prior failure to nonnucleoside analogues.

PATIENTS & METHODS

- All HIV-1 infected patients on regular follow-up at our clinic who had failed NNRTI-based regimens since January 1999 were identified.

- Genetic sequence analysis of the pol gene was performed and drug resistance mutations were interpreted following the latest International AIDS Society-USA panel list (www.iasusa.org, last update spring 2008).

- The following 14 RAMs were considered for etravirine: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, and G190S.

The list of NNRTI RAMs was as follows: A98G, L100I, L100V, K101E, K101H, K101I, K101N, K101P, K101Q, K103H, K103N, K103R, K103S, K103T, V106A, V106M, V108I, E138G, E138K, E138Q, V179D, V179E, V179F, V179G, V179I, Y181C, Y181I, Y181V, Y188C, Y188F, Y188H, Y188L, G190A, G190C, G190E, G190Q, G190S, H221Y, P225H, F227C, M230I, M230L, K238N, K238T and Y318F.

- Mutations in the connection domains of the reverse transcriptase (N348I, T369I, and E399D) were also considered in the analysis.

- Drug resistance phenotyping was examined using a commercial phenotypic assay (Antivirogram, VIRCO, Mechelen, Belgium). The level of phenotypic resistance was expressed as the fold change in 50% inhibitory concentration compared with a wild-type reference virus. The lower clinical cut-off (LCCO) for etravirine was recently established as 3.

RESULTS

- Plasma specimens from a total of 40 individuals who had failed NNRTI in the past and mostly harboring at least one etravirine resistance mutation were tested. Viruses harbored different patterns of NNRTI RAM.

- All but one specimens belonged to individuals infected with HIV-1 subtype B. The other individual was infected with a subtype G strain.

- The rate of distinct etravirine RAM in this population was as follows:

V90I	5%
A98G	12.5%
L100I	2.5%
K101E	30%
V106I	12.5%
V179D	12.5%
Y181C	47.5%
G190A	47.5%
G190S	17.5%

- Overall, 70% of samples harboured less than three etravirine RAMs.

- Phenotypic results could be obtained from all samples. For 19 samples, the fold change was below the LCCO of 3; their median fold change value was 0.9 [IQR: 0.6-2.0]. In contrast, for 21 samples, the fold change was above 3; their median fold change was 9.3 [IQR: 6.1-13.1] (**table 1**).

- Most genotypes (75%) with 0 or 1 etravirine RAM had fold change below the etravirine LCCO. Conversely, 27.7% of specimens with at least 3 etravirine RAM had a fold change below LCCO. Y181C mostly along with one or more etravirine RAM showed a fold change above 3 (median 12.6).

- Two novel changes were found to be associated with a significant reduction in etravirine susceptibility. It was estimated to be 39.1-fold for K101H and 14.4-fold for E399D.

Table 1. Susceptibility to etravirine in specimens from 40 HIV-1 patients with prior failure to NNRTIs.

Mutations patterns with susceptibility to ETR	No. of ETR RAM	Phenotype FC to ETR	Mutations patterns with reduced susceptibility to ETR	No. Of ETR RAM	Phenotype FC to ETR
A98G, K101E, G190A	3	0.9	K101E, V108I, Y181C, G190A	3	24.4
V90I, K103N, Y181C, G190A, N348I	3	2.2	K101E, Y181C, G190A	3	10.8
K103N, Y181C	1	1.9	K101E, Y181C, G190S	3	8.2
K103N, G190A	1	0.8	K101E, K103R, Y181C, G190A	3	6.6
A98S, K101E, G190A	2	0.5	A98G, K101E, Y181C, G190A	4	3
G190A, N348I	1	2.9	Y181C, G190S	2	5.4
G190A	1	0.6	A98G, K103R, V108I, V179E, Y181C, G190A, E399D	3	29.3
G190S	1	0.3	A98G, K101E, Y181C, G190A	4	3.5
G190S	1	0.4	Y181C	1	3.3
K101E, G190S	2	0.6	Y181C, E399D	1	10.6
V106I, V179E, Y188L	1	2.2	K101H, Y181C, G190A	2	64.6
K101E, K103S, V108I, G190A	2	1.7	K101H, Y181C, G190A	2	13.7
K103R, V179D, G190A	2	2	L100I, K103N, G190A, K238T	2	9.3
K103R, V106I/M, V179D, G190A	3	2.4	Y181C, G190S, E399D	2	10.8
K103R, V179D	1	1.7	K101E, Y181C, G190S	3	23.4
V179D	1	0.9	V106I, Y188L, E399D	1	12.5
V179D	1	0.8	A98G, V106I, V179E, Y188L	2	8.8
K103N, V108I, Y318F, N348I, T369I	0	0.9	V106I, Y181C	2	7.4
A98S	0	1.4	K103E, K103N, Y181C, G190A, K238T, N348I	2	6
			V90I, V108I, Y181C, N348I	2	6.3
			G190E, E399D	0	11.1

ETR, etravirine; RAM, resistance associated mutations; FC, fold change.
ETR RAM are underlined. The lower clinical cut-off (LCCO) for ETR is 3.

CONCLUSIONS

- Although etravirine shows a relatively high genetic barrier for resistance, specific etravirine RAMs reduce the susceptibility to the drug more than others. This is the case of Y181C.

- The specific impact of each etravirine RAM should be weighted for a suitable genotypic resistance interpretation. The initial list of etravirine RAMs should be refined, including new mutations that influence etravirine susceptibility.