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Prevalence of genotypic and phenotypic susceptibility to etravirine in US samples received for routine resistance testing

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Abstract

Background

In the Phase III DUET trials of the NNRTI etravirine (ETR; TMC125), 77.0% and 74.1% of ETR-treated patients with a Tibotec susceptible ETR weighted genotypic score (WGS) ≤2 or an Antivirogram® fold-change (FC) ≤3 at baseline, respectively, achieved <50 HIV RNA copies/mL at Week 48. The prevalence of ETR susceptibility was investigated in clinical samples referred for routine resistance testing using Monogram Biosciences (MGR) ETR WGS and PhenoSense® assay.

Methods

Fourteen thousand, nine hundred and forty samples submitted to MGR for routine resistance testing from June 2008 to June 2009 were analysed. Samples were defined as NNRTI-resistant if they carried at least one of the following mutations: A98G, L100I, K101E, K101P, K103N, K103S, V106A, V106I, Y181x, Y188x, G190x, P225x, F227x, M230L and P236L, where x represents any amino acid substitution. MGR's ETR WGS consisting of 30 mutations[1] was used to define viral susceptibility to ETR, with a genotypic score ≤3 denoting full susceptibility. Phenotypic susceptibility to ETR was determined using 2.9 and 10 as low and high clinical cut-offs (CCOs), respectively. The impact of K103N on genotypic susceptibility to ETR was also investigated.

Results

Among 5,482 (36.7%) NNRTI-resistant samples, 67.2% were classified as genotypically susceptible and 76.4% as phenotypically susceptible (median FC 0.9) to ETR, with 10.7% having FC ≥10. Using Tibotec's WGS, 67.5% of NNRTI-resistant samples were ETR-susceptible (WGS ≤2). Among NNRTI-susceptible samples (n=9,458), 99.5% had ETR FC <2.9 (median 0.8) and 0.5% had FC ≥2.9 and <10 (median 3.5). In a subset of NNRTI-resistant samples (n=4,514), with (n=3,598) or without (n=1,884) the K103N mutation, the proportion of ETR genotypically-susceptible samples (average median FC 1) was 76.9% and 48.6%, respectively.

Conclusions

Using different interpretation systems, most samples received for routine resistance testing with or without evidence of NNRTI resistance were susceptible to ETR. Among NNRTI-resistant samples, more were ETR-susceptible phenotypically than genotypically, and more were ETR-susceptible among those with K103N.

Background and objectives

- ETR is a second-generation NNRTI with activity against efavirenz (EFV)- and nevirapine (NVP)-resistant clinical isolates
- In the Phase III DUET trials, 77.0% and 74.1% of ETR-treated patients with a Tibotec susceptible ETR WGS ≤2, or an Antivirogram® FC ≤3 at baseline, respectively, achieved <50 HIV RNA copies/mL at Week 48[2]
- The objective of this analysis was to investigate the prevalence of ETR susceptibility in clinical samples referred for routine resistance testing using the Tibotec ETR WGS and the MGR ETR WGS and PhenoSense® assay

Methods

- 14,940 samples submitted to MGR for routine resistance testing from June 2008 to June 2009 were analysed
- **Samples were defined as NNRTI-resistant genotypically if they carried at least one of the following mutations**
  - **A98G, L100I, K101E, K101P, K103N, K103S, V106A, V106I, Y181x, Y188x, G190x, P225x, F227x (where x = any amino acid substitution), M230L and P236L**
- MGR's ETR WGS consisting of 30 mutations[1] was used to define genotypic susceptibility to ETR
  - a score ≤3 denotes full genotypic susceptibility
- Tibotec's ETR WGS consisted of 17 ETR resistance-associated mutations (RAMs), where a score of ≤2 denotes full genotypic susceptibility to ETR[2]
- Phenotypic susceptibility to ETR was determined using the PhenoSense® assay
  - lower CCO 2.9, upper CCO 10
- The impact of K103N on genotypic susceptibility to ETR was investigated

ETR WGS scoring

- The ETR WGS was calculated by cumulative addition of the following mutations when present in the viral isolate, using the individual weightings in parentheses
  - **MGR WGS:**[1] *V90I* (1), *L100I* (4), *K101E* (2), *K101H* (1), *K101P* (4), V106A (2), V106M (1), *E138A* (3), E138G (3), E138K (2), E138Q (1), *V179D* (1), V179E (3), *V179F* (1), V179L (2), V179M (1), *Y181C* (4), Y181F (1), *Y181I* (4), *Y181V* (4), Y188L (2), V189I (1), G190E (1), G190Q (3), G190T (1), H221Y (1), P225H (1), *M230L* (3), K238N (3) and K238T (1)
  - **Tibotec WGS:**[2] *V90I* (1), A98G (1), *L100I* (2.5), *K101E* (1), *K101H* (1), *K101P* (2.5), V106I (1.5), *E138A* (1.5), *V179D* (1), *V179F* (1.5), V179T (1), *Y181C* (2.5), *Y181I* (3), *Y181V* (3), G190A (1), G190S (1.5) and *M230L* (2.5)

Italics indicate mutations used in both scoring systems

Frequency of all ETR mutations (MGR and Tibotec WGS)

ETR mutation: MGR WGS	ETR mutation: Tibotec WGS	Number of samples	Proportion of samples (%)	ETR mutation: MGR WGS	ETR mutation: Tibotec WGS	Number of samples	Proportion of samples (%)
V90I	V90I	952	6.4		V179T	54	0.4
	A98G	374	2.5	Y181C	Y181C	981	6.6
L100I	L100I	413	2.8	Y181F		18	0.1
K101E	K101E	413	2.8	Y181I	Y181I	49	0.3
K101H	K101H	90	0.6	Y181V	Y181V	26	0.2
K101P	K101P	109	0.7	Y188L		391	2.6
V106A		79	0.5	Y189I		370	2.5
	V106I	600	4.0		G190A	761	5.1
V106M		68	0.5	G190E		19	0.1
E138A	E138A	411	2.8	G190Q		16	0.1
E138G		118	0.8		G190S	160	1.1
E138K		85	0.6	G190T		7	0.1
E138Q		71	0.5	H221Y		444	3.0
V179D	V179D	362	2.4	P225H		574	3.8
V179E		174	1.2	M230L	M230L	68	0.5
V179F	V179F	30	0.2	K238N		30	0.2
V179L		28	0.2	K238T		263	1.8
V179M		28	0.2				

The five highest frequency ETR mutations (regardless of WGS) are shown in the rows shaded blue from a total of 35 mutations in the 14,940 samples received between June 2008 and June 2009

MGR ETR WGS in samples with NNRTI resistance

- Among the 5,482 (36.7%) samples with resistance to EFV or NVP, 67.2% were classified as genotypically susceptible to ETR using the MGR ETR WGS[1]

MGR ETR WGS[1]	Number of samples	Proportion of samples (%)
0	2,142	39.1
1	787	14.4
2	510	9.3
3	243	4.4
4	735	13.4
5	502	9.2
≥6	563	10.3
	N=5,482	

67.2% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

Tibotec ETR WGS in samples with NNRTI resistance

- Using Tibotec's WGS,[2] 67.5% of samples with resistance to EFV or NVP were classified as genotypically susceptible to ETR (WGS ≤2)

Tibotec ETR WGS[1]	Number of samples	Proportion of samples (%)
0	2,469	45.0
0.5–1	857	15.6
1.5–2	372	6.8
2.5–3.5	1,335	24.4
4–4.5	216	3.9
5–5.5	132	2.4
≥6	101	1.8
	N=5,482	

67.5% susceptible to ETR

Scores 0–2 denote full ETR susceptibility; scores ≥2.5 denote reduced ETR susceptibility

MGR ETR FC in samples with NNRTI resistance

- Among 5,482 samples with resistance to EFV or NVP, 76.4% were classified as phenotypically susceptible to ETR (median FC 0.9) based on the MGR ETR FC, with 10.7% having FC ≥10

MGR ETR FC	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC
<2.9	4,187	76.4	0.9	0.6	1.2	0.3	2.2
≥2.9, <10	709	12.9	5.0	3.7	6.9	3.0	9.2
≥10	586	10.7	24.5	14.7	54.3	10.7	200
	N=5,482						

76.4% susceptible to ETR

FC <2.9 denotes full ETR susceptibility; FC ≥2.9 denotes reduced ETR susceptibility; Q = quartile

MGR ETR FC in NNRTI-susceptible samples

- Among 9,458 NNRTI-susceptible* samples, 99.5% had ETR FC <2.9 (median FC 0.8) and 0.5% had FC ≥2.9 and <10 (median FC 3.5) based on the MGR ETR FC

MGR ETR FC	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC
<2.9	9,409	**99.5**	0.8	0.6	1.0	0.3	1.5
≥2.9, <10	49	**0.5**	3.5	3.1	4.3	3.0	6.5
≥10	0	N/A	N/A	N/A	N/A	N/A	N/A
	N=9,458						

99.5% susceptible to ETR

- The frequency of reverse transcriptase mutations in these subgroups is described on the following slide

FC <2.9 denotes full ETR susceptibility; FC ≥2.9 denotes reduced ETR susceptibility
*Without any of the mutations defined on the Methods slide; N/A = not applicable

Frequency of reverse transcriptase mutations in NNRTI-susceptible samples

- Mutations were observed among the 49 (0.5%) samples with no NNRTI resistance* but with ETR FC ≥2.9 and <10 (median FC 3.5)

NNRTI RAM	Number of samples	Proportion of samples (%): Based on NNRTI-susceptible samples with ETR FC ≥2.9 <10 (n=49)	Proportion of samples (%): Based on all NNRTI-susceptible samples (n=9,458)
E138G	2	4.1	0.02
E138K	2	4.1	0.02
E138Q	1	2.0	0.01
E138A (including mixture)	35	71.4	0.37
V179E	3	6.1	0.03
V179D	2	4.1	0.02
V90I	2	4.1	0.02
V106I	1	2.0	0.01
No mutations*	1	2.0	0.01
	N=49		

- For the remaining 9,409 NNRTI-susceptible samples (with ETR FC <2.9), there were 454 samples with mutations at E138

*Without any of the mutations defined on the Methods slide

MGR ETR WGS in samples with K103N mutation

- In a subset of NNRTI-resistant samples with the K103N mutation (N=3,598), the proportion of ETR genotypically-susceptible samples (average median FC 1) was 76.9% based on the MGR ETR WGS[1]
- Similar results were obtained with Tibotec's WGS[2] (77.5%)

MGR ETR WGS[1]	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC
0	1,776	49.4	0.8	0.5	1.0	0.3	1.6
1	652	18.1	0.9	0.6	1.2	0.3	2.0
2	208	5.8	1.2	0.8	1.9	0.4	5.9
3	130	3.6	1.2	0.8	2.3	0.4	9.2
4	387	10.8	4.3	1.8	8.8	0.7	32.2
5	248	6.9	5.0	2.0	13.3	0.6	47.8
≥6	197	5.5	11.6	3.7	35.6	1.2	200
	N=3,598						

76.9% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

MGR ETR WGS in samples without K103N mutation

- In a subset of NNRTI-resistant samples without the K103N mutation (N=1,884), the proportion of ETR genotypically-susceptible samples (average median FC 1) was 48.6% based on the MGR ETR WGS[1]
- Similar results were obtained with Tibotec's WGS[2] (48.2%)

MGR ETR WGS[1]	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC
0	366	19.4	0.7	0.4	0.9	0.2	1.4
1	135	7.2	0.7	0.4	1.1	0.2	2.6
2	302	16.0	1.1	0.7	2.0	0.4	7.0
3	113	6.0	1.5	1.0	2.9	0.5	9.6
4	348	18.5	2.5	1.4	5.5	0.6	38.1
5	254	13.5	4.2	2.0	10.2	0.9	69.0
≥6	366	19.4	8.9	3.0	30.6	1.1	200
	N=1,884						

48.6% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

Conclusions

- Using different interpretation systems, most samples received for resistance testing, with or without evidence of NNRTI resistance, were susceptible to ETR
- The five most frequent ETR mutations in this dataset (regardless of WGS) were
  – Y181C, V90I, G190A, V106I and P225H
- Among NNRTI-resistant samples, more were ETR-susceptible phenotypically than genotypically, and more were ETR-susceptible among those with K103N
- Among NNRTI-susceptible samples, modest increases in ETR FC above the lower CCO were associated primarily with the presence of mutations at position 138 – however, the majority of samples with an E138A mutation were phenotypically susceptible to ETR

References

1. Benhamida J, et al. Antivir Ther 2008;13(Suppl. 3). A142.
2. Vingerhoets J, et al. AIDS 2010;24:503–14.

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