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) \( \leq 2 \) or an Antivirogram® fold-change (FC) \( \leq 3 \) 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, 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 was used to define viral susceptibility to ETR, with a genotypic score \( \leq 3 \) 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 \( \geq 10 \). Using Tibotec's WGS, 67.5% of NNRTI-resistant samples were ETR-susceptible (WGS \( \leq 2 \)). Among NNRTI-susceptible samples (n=9,458), 99.5% had ETR FC <2.9 (median 0.8) and 0.5% had FC \( \geq 2.9 \) 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. 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.

Methods

ETR WGS scoring

- The ITUN WGS was calculated by cumulative addition of the following mutations to the viral load, using the individual drug targets for etravirine:

Frequency of all ETR mutations

- Among 14,940 samples, 67.5% were classified as genotypically susceptible to ETR (WGS \( \leq 2 \)).

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


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