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EXPLORING ETRAVIRINE RESISTANCE AMONG RECENT ROUTINE CLINICAL SAMPLES SUBMITTED FOR RESISTANCE TESTING

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BACKGROUND: Phenotypic susceptibility to efavirenz and nevirapine is significantly affected by single mutations in the viral genome resulting in increased fold-change values and loss of clinical efficacy. In the DUET and other trials, etravirine has demonstrated significant clinical efficacy in patients with virus strains resistant to the first generation non-nucleoside reverse transcriptase inhibitors (NNRTIs). In those trials, baseline etravirine phenotypic susceptibility was a strong predictor of virological response. We evaluated etravirine susceptibility among a large dataset of recent routine clinical samples (RCS).

METHODS: Phenotypic susceptibility to NNRTIs (fold change in 50% inhibitory concentration, FC) was calculated from the viral genotype (vircoTYPE v4.2.01) for 93,500 samples submitted to Virco for routine resistance analysis between January 2005 and November 2007. A subset of samples with genotypic evidence of NNRTI resistance was identified. Etravirine FC values were classified as maximal response (MA), reduced response (RR) or minimal response (Min) based on vircoTYPE clinical cutoffs of 1.6 (CCO1) and 27.6 (CCO2) associated with 20% and 80% loss of the predicted wild-type response. Because the RR category spans a broad FC range, a further subdivision based on an etravirine FC of 5.0, associated with a 50% loss of response, was explored.

RESULTS: Among RCS, 73.3%, 24.3% and 2.4% had ETR FC values classified as MA, RR, or Min, respectively. An ETR FC of ≤ 5.0 was observed in 89.8% of RCS. At least one NNRTI-resistance-associated mutation was detected in 38.4% of RCS. Among these NNRTI-resistant samples, 47.9%, 46.5% and 5.6% had ETR FC values classified as MA, RR, or Min, respectively, and 74.4% had an ETR FC ≤ 5.0 . Among samples in the etravirine RR category, 67.6% of all RCS, and 57% of samples with NNRTI mutations had etravirine FC ≤ 5.0 . In the Duet studies, virological response (undetectable viral load at Week 24) was observed in 69%, 59%, 49%, and 44% of individuals with baseline ETR FC < 1.6 , 1.6 to ≤ 5 , 5 to ≤ 27.6 , and > 27.6 , respectively.

CONCLUSIONS: Most RCS, including those with evidence of resistance to first generation NNRTIs, had low ETR FC values, suggesting they might benefit from treatment with etravirine as part of a HAART regimen.

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