

SATuRN: Preliminary report 2011

Southern Africa Treatment and Resistance Network

Phenotypic Resistance to Etravirine in an HIV-1 Subtype-C Background

Background: South Africa has an estimated 5.7 million people infected with HIV-1 of whom 919,923 were receiving antiretroviral treatment by the end of 2009. The first-line regimen includes a non-nucleoside reverse transcriptase inhibitor (NNRTI), either efavirenz or nevirapine. Both drugs share similar mutation profiles and exhibit cross-resistance. Here we examine the phenotypic sensitivity of single and double NNRTI mutations found in patients failing either nevirapine or efavirenz, to a second generation NNRTI, etravirine which has an unrelated resistance profile.

Methods: Single and double NNRTI resistance mutations were introduced into an HIV-1 expression plasmid containing a ~3.7 kilo-base *gag-pol* insert from a subtype-C reference strain. The NNRTI mutation list from the International AIDS Society was used for selection of single mutants. Double mutants with significant covariation were identified by performing a Jaccard analysis on sequences from NNRTI experienced patients. Mutant plasmids were transfected into 293T-cells for the production of HIV-1 resistance vectors, and used to infect 293T-cells in serial dilutions of efavirenz, nevirapine and etravirine. Fold-change (FC) values were deduced for each virus-drug combination. Phenotypic resistance was classified by use of the Monogram PhenoSense™ and Virco Antivirogram® cut-off values.

Results: Of the 30 single NNRTI mutations tested, only Y181I (FC>40) and Y181V (FC>40) caused high level resistance to etravirine. Mutations K101E/P, E138A/K, Y181C, Y188L and M230L gave a low to intermediate level of resistance. Mutations K101P, K103N, V106M, Y188L, G190S and M230L caused high-level resistance to efavirenz and nevirapine, while Y181C/I/V, Y188C/L and G190S conferred high-level resistance to nevirapine only. Mutation V179F conferred hyper-susceptibility to all three NNRTIs (FC=0.004-0.151). Mutation Y188C, although conferring high level resistance to nevirapine (FC>40), conferred hypersusceptibility to etravirine (FC=0.144). All eight double mutations caused high-level resistance to nevirapine (FC>40), and some to efavirenz. Interestingly, the combination of V179F with Y181C caused a high level of resistance to both etravirine (FC=>40) and nevirapine (FC>40). The Y181C and G190S double mutant was the only other combination that caused high-level resistance to etravirine (FC>40).

Conclusion: NNRTI resistance mutations, either singly or in combination, that arise in response to nevirapine or efavirenz rarely conferred high levels of resistance to etravirine. However, the combinations of V179F/Y181C and G190S/Y188C conferred high level resistance to ETV, as has previously been predicted. As combinations are not prevalent in currently failing individuals, etravirine is a suitable option for first-line NNRTI-based regimen salvage.

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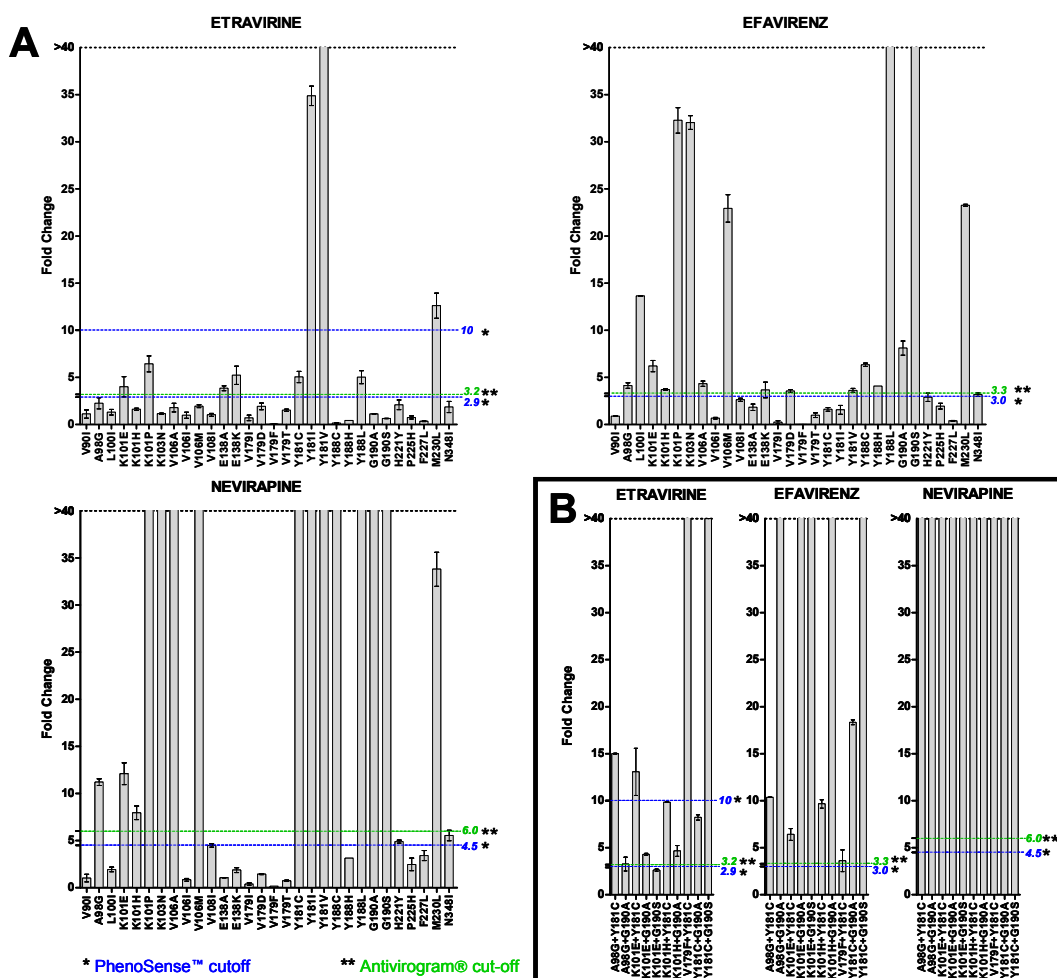


Figure: Phenotypic resistance of (A) single and (B) double NNRTI mutants to etravirine, nevirapine and efavirenz. Resistant pseudovirions, containing one or two NNRTI mutations, were produced by transfection into 293T cells. Pseudovirions were tested against serial dilutions of efavirenz, nevirapine and etravirine. The IC₅₀-values of each drug-virus combination were compared to that of the MJ4 wild-type control and Fold-Change (FC) values were obtained. Cut-off values for both Monogram PhenoSense and Virco Antivirogram are indicated on the graphs.

Reference:

AE Basson, S-Y Rhee, CM Parry, T de Oliveira, D Pillay, R Shafer and L Morris. Poster Presentation, International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies, June 7-11, 2011, Los Cabos, Mexico