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HIV replicative capacity / fitness

The COLATE trial: comparison of the evolutionary distance for protease and reverse transcriptase sequences

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Virological failure on a regimen containing lamivudine (3TC) is associated with emergence of the M184I/V mutation. Previous studies suggest a higher fidelity of the mutant reverse transcriptase. Hypothetically, the presence of the M184I/V mutation would lead to a reduced rate over time in number of other mutations for patients continuing 3TC compared to those discontinuing 3TC.

Cryopreserved plasma samples from the COLATE trial, in which patients failing a 3TC containing regimen (HIV-RNA >1000 c/ml) were randomised to continue (3TC arm) or discontinue 3TC (No-3TC arm) whilst continuing a three-drug regimen, were used for protease and reverse transcriptase sequencing on all available samples at baseline and during follow-up (with HIV-RNA >500 c/ml)(patients included if sequences at baseline and >1 follow-up visit was available). Phylogenetic trees were created using the Neighbour-Joining distance method and the PAUP program was used to calculate the number of changed nucleotides since baseline (Jukes-Cantor distance).

A total of 67 sequences in 19 patients (3TC arm) and 67 sequences in 23 patients (No-3TC arm) were obtained. Sequences were 1302 nucleotides long. Four sequences in 4 patients in the No-3TC arm and 1 in the 3TC arm were outliers in the phylogenetic tree. These patients were excluded from the analyses so that the evolutionary drift from baseline could be measured for the remaining patients without the interference of the outliers. The Jukes-Cantor distances show an increase in number of nucleotide changes from baseline to week 48, comparable between the two arms at all time points; e.g. at Week 48 the median [IQR] nucleotide distances from baseline were 2.01 [0.00, 17.41](n=9) and 4.05 [1.01, 11.22](n=7) in the 3TC arm and the No-3TC arm, respectively (p=0.49). Similar results were found using the Kimura 2-parameter (1.54 [0.00, 13.39] vs. 3.11 [0.78, 8.63]; p=0.49) and the SynScan synonymous/non-synonymous method (5.2 [1.3, 11.8] vs. 5.5 [2.7, 8.5]; p=0.67).

In this substudy to the COLATE trial comparable mutation rates were found over 48 weeks among patients failing a 3TC-containing regimen who either continued or discontinued 3TC as part of HAART.