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## INFLUENCE OF NEW REVERSE TRANSCRIPTASE MUTATIONS ON VIROLOGICAL RESPONSE TO DIDANOSINE IN THE DIDANOSINE ADD ON JAGUAR STUDY

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**BACKGROUND:** It has been shown recently that a genotypic score (GS) (+M41L +T69D -K70R +L74V -M184V/I +T215Y/F +K219Q/E) including known drug resistance mutations impacting negatively and positively the response to didanosine (ddI), allows to define resistance ( $GS \geq +2$ ) and non resistance ( $GS \leq +1$ ) to ddI in pre-treated patients. The additional impact of other reverse transcriptase (RT) mutations, such as polymorphism at amino acid residues, remains to be explored.

**METHODS:** One-hundred-and-eleven patients experiencing virological failure were randomized to receive ddI in addition to their current combination therapy for 4 weeks. For each codon along the RT gene (21–236, except those previously investigated to build in the GS), reduction in HIV-1 RNA at week 4 (primary endpoint of the study) was compared in patients with and without mutation. This was an exploratory analysis and mutations that provide P-values lower than 0.01 were retained as likely related to ddI response. A "polymorphism score" (PS) was defined from the sum of the retained mutations and its potential added value to the GS was tested. Non parametric tests were used.

**RESULTS:** Three mutations (H208Y, R211A/D/G/K/S, L214F, L228H/M/R) were associated with a poorer virological response to ddI and one (L214F) with better virological response ( $P < 0.01$ ); so the PS was comprised between -1 and +3. Among non resistant patients ( $GS \leq +1$ ), median HIV-1 RNA reduction was -1.18 ( $n=16$ ), -0.66 ( $n=25$ ), -0.39 ( $n=29$ ), -0.41 ( $n=7$ ), and -0.26 ( $n=1$ )  $\log_{10}$  copies/mL, according to the PS ( $P < 0.001$ ). Among resistant patients ( $GS \geq +2$ ), there was no added value of the PS to the

GS ( $P=0.11$ ). Variants at position 211 and 214 were found associated ( $P<0.001$ ) with variants at position 41 and 70, respectively, while variant F at position 214 was found associated ( $P<0.001$ ) with wild type at position 41 and 215.

**CONCLUSION:** With a stringent criterion, four mutations (H208Y, R211A/D/G/K/S, L214F, L228H/M/R) appear to be associated with virological response to ddI therapy. Taking account of these mutations, in addition to the GS, this may improve the classification of patients defined as not resistant to ddI and to better discriminate them. Nevertheless, this approach should be further investigated in other studies or databases.

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