

12th International HIV Drug Resistance Workshop



10–14 June 2003, Cabo del Sol, Los Cabos, Mexico

HIV-1 REVERSE TRANSCRIPTASE MUTATIONS THAT SUPPRESS ZIDOVUDINE RESISTANCE ALSO INCREASE *IN VITRO* SUSCEPTIBILITY TO TENOFOVIR, BUT NOT STAVUDINE

Antivir Ther. 2003; 8:S34 (abstract no. 29)

NT Parkin, C Chappey, CJ Petropoulos and N Hellmann
ViroLogic, Inc., South San Francisco, Calif., USA

BACKGROUND: Susceptibility of HIV-1 to zidovudine is increased by at least five mutations in reverse transcriptase (RT): K65R, L74V, L100I, Y181C and M184V. In some cases these 'suppressive mutations' restore susceptibility to zidovudine despite of the presence of resistance mutations such as K70R or T215F/Y. In general, susceptibility to stavudine and tenofovir is modulated by RT resistance mutations in a manner that qualitatively parallels that of zidovudine. Thus, we evaluated the effect of suppressive mutations on susceptibility to stavudine and tenofovir.

METHODS: A clinical sample database of over 16,000 matched genotypes and phenotypes was queried for samples containing T215F or Y without, or with one or more, suppressive mutations (K65R, L74I and V, L100I, Y181C, I, and V, and M184I and V; different variants at each position were grouped together). Samples containing multi-nucleoside RT inhibitor (NRTI) resistance mutations (T69ins or Q151M) were excluded, as were samples with mixtures at positions that were part of the query. NRTI fold change (FC) in IC₅₀ vs NL4-3 reference was compared between groups of viruses using the Mann-Whitney non-parametric test.

RESULTS: Median zidovudine FC for T215Y/F samples with no suppressive mutations ($n=966$), L74I/V alone (that is, no other suppressive mutations, $n=87$), L100I alone ($n=54$), Y181I/C/V alone ($n=283$) or M184I/V alone ($n=1423$) was 145-, 102-, 78-, 75- and 12-fold, respectively ($P<0.05$ for each suppressive mutation group vs no suppressive mutations). The corresponding FC values for tenofovir were 2.8-, 2.2-, 2.1-, 2.4- and 1.3-fold, respectively (all $P<0.05$), and for stavudine were 2.4-, 3.3-, 2.5-, 2.8- and 1.8-fold, respectively (all $P<0.05$ except L100I). The number of samples with K65R and T215F/Y was too low to provide meaningful comparisons. Combinations of two or more suppressive mutations were generally additive in suppressing zidovudine and tenofovir

resistance. For example, median zidovudine and tenofovir FC for samples with L100I+M184IV ($n=28$) were 3.8- and 0.8-fold, and for Y181I/C/V+M184I/V ($n=174$) were 10- and 1.1-fold, respectively. Lower FC in groups with suppressive mutations could not be explained by fewer thymidine analogue mutations (median number 3 to 4 for all groups). As expected, FC for didanosine, zalcitabine (ddC) and abacavir was higher in groups containing L74I/V and/or M184I/V, and was not significantly affected by L100I or Y181C/I/V.

CONCLUSIONS: M184I/V increases susceptibility to zidovudine, tenofovir and stavudine. Other suppressive mutations in RT affect tenofovir and zidovudine, but not stavudine. Susceptibility to stavudine decreased in the presence of L74I/V and Y181I/C/V. Additive effects were observed when suppressive mutations were present together. Combined mutations were capable of re-sensitizing tenofovir ($FC < 1.4$) and zidovudine ($FC < 2.5$) in the presence of multiple thymidine analogue mutations. Since genotype interpretation algorithms do not account for the effects of most suppressive mutations, these observations provide an explanation for phenotype/genotype discordance for zidovudine and tenofovir.

PRESENTING AUTHOR: NT Parkin

2003-07-08
29

Copyright © 2003 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.