

15th International HIV Drug Resistance Workshop



13-17 June 2006, Sitges, Spain

PATTERNS OF TIPRANAVIR SUSCEPTIBILITY AND CROSS-RESISTANCE AMONG PATIENT SAMPLES SUBMITTED FOR ROUTINE RESISTANCE TESTING

Antivir Ther. 2006, 11:S35 (abstract no. 30)

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BACKGROUND: Tipranavir, the most recently approved protease inhibitor (PI), has a favorable activity profile among viruses resistant to other PIs. However the relative degree of cross-resistance between tipranavir and other PIs and in samples containing mutation clusters selected by other PIs is not fully understood.

METHODS: We used a database containing phenotype (PhenoSense HIV) and genotype (GeneSeq HIV) results for 3845 samples containing at least one PI-selected mutation, submitted to the Monogram Clinical Reference Laboratory for routine resistance testing, to characterize prevalence and patterns of tipranavir resistance and PI cross-resistance. Samples were classified as tipranavir sensitive (S), partially sensitive (PS), or resistant (R) if the fold change in IC_{50} (FC) was less than 2, 2 to 8, or over 8-fold, respectively.

RESULTS: In the complete data set, 62%, 25%, and 13% of samples were S, PS, or R to tipranavir. Linear regression coefficients (R squared) using log-transformed FC values between tipranavir and other PIs were as follows: 0.41, 0.40, 0.27, 0.45, 0.30, 0.40, and 0.42 for amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, and atazanavir, respectively. Among samples PS to tipranavir, the percentage S to other PIs, using updated lower clinical cutoffs for boosted PI regimens, was as follows: 19% for amprenavir, 26% for indinavir, 12% for saquinavir, 17% for lopinavir, 11% for atazanavir. Of samples PS to lopinavir, 48% were susceptible to tipranavir. The median FC (MFC) to tipranavir was less than 2 in samples containing only one primary mutation except V82L (MFC 2.4, $n=4$); the percentage of samples that were PS to tipranavir was over 25% for I84V and V82L. Tipranavir MFC was elevated (2.1 to 2.8) in samples with the following mutation combinations: V32I/M46IL/I47V, I54V/V82A/L90M, and M46IL/I54V/V82A/L90M ($n=5$, 85, and 56, respectively). In these 3 groups,

approximately 50–60% of samples had partial tipranavir sensitivity, but fewer than 13% were fully resistant.

CONCLUSIONS: Cross resistance between tipranavir and other approved PIs is lowest with nelfinavir and saquinavir, highest with amprenavir and atazanavir, but modest in any case. Viruses with single primary mutations remain largely sensitive to tipranavir, with the exception of I84V and V82L.

2006-06-13
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