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## CHARACTERIZATION OF HIV-1 SHOWING DECREASED SUSCEPTIBILITY TO TIPRANAVIR AND THEIR INHIBITION BY TIPRANAVIR-CONTAINING DRUG MIXTURES

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**BACKGROUND:** Tipranavir (TPV) is a non-peptidic protease inhibitor that maintains potent activity against a broad range of multiple protease inhibitor resistant human immunodeficiency virus (HIV-1) isolates. The genotypic changes responsible for the reduced susceptibility to TPV and their effect on cross resistance to other PIs are only partially understood. Here we present our characterization of TPV-resistant viruses at the genotypic and phenotypic levels including their *in vitro* susceptibility to inhibition by mixtures of the protease inhibitors TPV:amprenavir (APV) or TPV:lopinavir (LPV).

**METHODS:** Recombinant viruses were reconstructed to represent HIV-1 selected to grow in culture in the presence of TPV or representing clinical isolates from patients undergoing therapy with TPV. Viruses contained between 2–17 mutations in the protease gene and in some cases an additional mutation in the CA/P2 p55<sup>gag</sup> cleavage site. Viruses were studied in antiviral assays to determine their susceptibility to protease inhibitors and in a Jurkat-LTR luciferase reporter cell line to determine their replication capacity. Susceptibility to inhibition by TPV containing drug mixtures was determined using constant ratio combination experiments and the calculation of combination indices (CI). Using this model, CI values <0.9=synergy, CI between 0.9 and 1.1=additive effects (no drug interaction) and CI>1.1=antagonism.

**RESULTS:** *In vitro* selected TPV-resistant viruses contain up to 10 mutations in the protease gene, including L33F, V82L and I84V. Introduction of these mutations into viral molecular clones by site-directed mutagenesis conferred up to 69-fold resistance to TPV and two- to 118-fold decreased susceptibility to other protease inhibitors in addition to decreasing viral replication capacity. A CA/P2 cleavage site mutation observed during *in vitro* selection did not directly contribute to TPV resistance. The following two clinical

protease genotypes were found to confer five- and seven-fold decreased susceptibility to TPV, respectively: V3I/L10V/I15V/L19I/M36L/S37N/R41K/M46I/K55R/Q61N/I64V/I72V/T74S/V82T/I84V/I85V/I93L and V3I/L10V/L33I/E35D/M36I/S37N/I54V/Q58E/I62V/L63P/A71V/V82L/L90M/I93L/C95V. Drug mixture experiments using these clinical isolate-derived viruses or wild-type HIV-1 showed that combinations of TPV:APV and TPV:LPV displayed predominantly additive effects against wild-type virus replication and somewhat lower CIs against protease mutant viruses. However, only in a few instances was the deviation from the additive effect outside the inter-experimental variability.

**CONCLUSIONS:** Resistance to TPV involves multiple mutations in the protease gene and leads to a reduced sensitivity to most other PIs and to a decreased replication capacity of viruses. TPV, however, maintains mostly additive effects on TPV-resistant or wild-type virus when used in combination with the protease inhibitors APV and LPV.

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