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PHENOTYPIC AND GENOTYPIC RESISTANCE TO A NEW PROTEASE INHIBITOR, 640385, IN HIV-1 VIRUS SAMPLES FROM SUBJECTS FAILING AMPRENAVIR

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BACKGROUND: 640385 is a new protease inhibitor (PI) in clinical development with potency against multiple PI-resistant clinical isolates. Because 640385 shares structural features with amprenavir, early assessment of any potential cross-resistance was desirable. HIV-1 isolates from subjects experiencing virological failure on amprenavir-containing regimens were examined for resistance to 640385 and amprenavir.

METHODS: Thirty clinical isolates obtained from subjects experiencing virological failure to an amprenavir-containing regimen and having amprenavir-associated resistance mutations (I54L/M $n=10$, I50V $n=10$, V32I+I47V $n=5$, I84V $n=2$, V32I $n=1$, I54L+I84V $n=1$, I54M+I84V $n=1$) were sent to ViroLogic for phenotypic evaluation (PhenoSense™). Isolates had additional protease substitutions (mean of 3.7 IAS mutations, mean of 7.9 changes from HXB2). Isolates containing mixtures at amprenavir-associated amino acid positions were excluded.

RESULTS: The mean fold increase of IC_{50} for the 30 viruses was 10.8-fold change (FC) to amprenavir and 2.0-FC to 640385. Of the 13 viruses (13/30, 43%) with >10-FC to amprenavir (mean 17.7-FC), none (0/13, 0%) had >10-FC to 640385 (mean 3.1-FC). Of the 17 (17/30, 57%) viruses with ≤ 10 -FC to amprenavir (mean 5.5-FC), none (0/17, 0%) had >2 FC to 640385 (mean 1.2-FC). Of the viruses harbouring I54L/M or V32I+I47V mutations, none had >2-FC to 640385 (I54L/M: amprenavir mean 4.7-FC vs 640385 1.1-FC; V32I+I47V amprenavir mean 8.8-FC vs 640385 1.4-FC). Of the viruses harbouring the I50V mutation, 5/10 had <2-FC, 4/10 had 2 to ≤ 3 -FC and 1/10 had >3-FC (7.9-FC) to 640385 (I50V: amprenavir mean 13.4-FC vs 640385 2.7-FC). Viruses harbouring the I84V mutation in the absence of other amprenavir-associated mutations had limited reduction in susceptibility to 640385 (1.4- and 2.1-FC). Both viruses having the I54L/M+I84V mutations had >3-FC to 640385 (3.9- and 6.0-FC, respectively).

CONCLUSIONS: In a panel of HIV-1 isolates specifically selected for presence of amprenavir resistance, there was minimal evidence for cross-resistance between 640385 and amprenavir despite their chemical similarity. Although I54L/M+I84V mutations may contribute to decreased 640385 susceptibility, I54L/M mutations in the absence of I84V, and conversely I84V mutations in the absence of I54L/M and V32I+I47V do not appear to be associated with 640385 resistance. Similarly, the I50V mutation did not appear associated with 640385 resistance.

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