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IN VITRO CROSS-RESISTANCE PROFILE FOR A NEXT- GENERATION NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR: IDX899

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BACKGROUND: IDX899 is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), which has demonstrated significant HIV-1 inhibition in treatment-naïve patients. Here we compare the *in vitro* resistance mutations elicited by IDX899, TMC125 (etravirine) and efavirenz (EFV) and profile the susceptibility of the resultant virus isolates to each of the three agents along with TMC278 (rilpivirine).

METHODS: Wild-type HIV-1 (BH10, subtype B) was passaged under increasing drug pressure to generate resistant mutant viruses. Viral supernatants were characterized by RT-PCR and direct population sequencing. Resistance and cross-resistance profiles were determined (as EC₅₀ shifts) for each viral supernatant.

RESULTS: As reported previously (Richman *et al.*, [Conf Retrovir Opportunistic Infect 2008 Feb 3-6;15: \(abstract no. 729\)](#), high level (>100-fold) resistance to efavirenz emerged rapidly, requiring just five to 13 passages and one to three mutations. In contrast, IDX899 and TMC125 resistance required more passages (25–30) and mutations (three to five). Selected mutations included: L100I, K103R, V179D, G190A, V35L and R83K (efavirenz); L100I, K103R, V179D/I, E138G, Y181C, K219R and R83K (TMC125); and V90I, E138K, Y181C/I, S134I, I135R, G190E and M230L (IDX899). All six efavirenz-selected virus isolates were highly (>100-fold) resistant to efavirenz; 4/6 isolates lost >10-fold susceptibility to TMC125 versus only 1/6 for both IDX899 and TMC278. For TMC125-selected isolates (containing up to five mutations), IDX899 retained good activity (< sixfold shift) against 9/10 isolates, compared with only 2/10 for efavirenz, 3/10 for TMC125 and 4/10 for TMC278. For IDX899-selected viruses, 6/8 showed a > sixfold loss of susceptibility to both IDX899 and TMC278, versus 7/8 for TMC125, and 5/8 for efavirenz. Efavirenz retained the best overall activity against the IDX899-selected isolates, whereas the TMC compounds were often less active than IDX899. Overall, of the 24 NNRTI-selected virus pools tested, 71% were <10-fold cross-resistant to IDX899 versus 25%, 38% and 67% for

efavirenz, TMC125 and TMC278, respectively. Moreover, the average EC₅₀ shift for IDX899 was five times less than that of TMC125.

CONCLUSIONS: IDX899 has previously been shown to be active against most of the resistance mutations produced by first-generation NNRTIs. The present study of NNRTI-selected mutants suggests that IDX899 has less *in vitro* cross-resistance than efavirenz and TMC125.

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