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TMC125 CAN SUPPRESS THE SELECTION OF RESISTANT HIV FROM A VIRUS POPULATION CARRYING THE K103N OR THE Y181C MUTATION

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BACKGROUND: TMC125 is a next generation nonnucleoside reverse transcriptase Inhibitor (NNRTI), highly active against wild-type and NNRTI-resistant HIV-1 strains. With wild-type HIV-1, selection of resistant virus *in vitro* in the presence of 200 nM TMC125 was delayed, as compared with first generation NNRTIs, and did not occur at all in the presence of 1 μ M TMC125. The selected viruses generally harboured two mutations. Similar experiments were conducted with HIV-1 strains containing key NNRTI resistance mutations, that is, K103N and Y181C, alone or in combination, in order to investigate further the genetic barrier for development of resistance to TMC125.

METHODS: *In vitro* selection experiments were conducted at a high multiplicity of infection (≥ 1 CCID₅₀/cell). MT-4 cells were infected with virus strains constructed by site-directed mutagenesis and carrying either the K103N or the Y181C mutation or both. Infected cells were cultured in the presence of 40, 200 or 1000 nM TMC125 and were monitored twice weekly for virus replication. Cultures without evidence of virus replication were further subcultivated in the presence of the same concentration of compound up to 30 days (10 passages).

RESULTS: In the presence of 40 nM TMC125, virus selected from the K103N mutant harboured the additional L100I/L and Y181C/Y mutations, and showed over 3000-fold decreased susceptibility to efavirenz, but less than 10-fold to TMC125. In the presence of 200 nM TMC125 virus breakthrough from the K103N mutant was observed in only one of two attempts after 21 days. The selected virus harboured the additional Y181C and M230I mutations, and exhibited a less than 10-fold increased EC₅₀ for TMC125. No virus breakthrough was observed at 1 μ M TMC125. Virus selected from the Y181C mutant in the presence of 40 or 200 nM TMC125 harboured changes at the 179 position, showed decreased susceptibility to TMC125 (5 and 90 FR, respectively), but remained sensitive

to efavirenz. Again, no virus breakthrough was observed at 1 μ M. Virus breakthrough was observed at all tested TMC125 concentrations with the K103N/Y181C double mutant strain. Viruses emerging in the presence of 200 nM TMC125 or higher all harboured the L100I mutation and other polymorphisms, and were highly resistant to TMC125 and efavirenz.

CONCLUSION: In a standardized *in vitro* selection protocol, NNRTI-resistant mutants carrying the K103N or the Y181C mutation behaved similarly to wild-type HIV-1, that is, no virus breakthrough was observed in the presence of 1 μ M TMC125. Selection of TMC125 resistant strains from the double K103N/Y181C mutant was comparable to the profiles observed with first generation NNRTIs when using wild-type HIV-1. These data confirm the existence of an increased genetic barrier to the development of resistance against TMC125.

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