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***IN VITRO* SELECTION EXPERIMENTS DEMONSTRATE AN INCREASED GENETIC BARRIER TO RESISTANCE DEVELOPMENT TO TMC114 AS COMPARED WITH CURRENTLY LICENSED PROTEASE INHIBITORS**

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BACKGROUND: TMC114 is a next generation HIV protease inhibitor (PI) highly active against wild-type and PI-resistant HIV. In order to compare the rate of emergence of resistance to TMC114 with those to amprenavir, nelfinavir or lopinavir, and to determine the sequence of mutations leading to reduced susceptibility to TMC114, *in vitro* selection experiments were performed.

METHODS: MT-4 cell cultures, infected at low multiplicity of infection (0.01–0.001 CCID₅₀/cell) with wild-type HIV-1/LAI in the presence of inhibitor, were monitored twice-a-week for virus replication. Infected cells were further subcultivated in the presence of the same concentration of inhibitor until full virus replication was observed. Escaping virus was further challenged with a two- to three-fold higher inhibitor concentration.

RESULTS: Comparison of the selection schedules of TMC114, amprenavir, nelfinavir and lopinavir showed two marked differences. Firstly, the selection process was most rapid with amprenavir and nelfinavir, slower with lopinavir, and slowest with TMC114. Secondly, viruses capable of replicating in the presence of 1 μ M inhibitor were selected by amprenavir after 30 days, nelfinavir after 20 days and lopinavir after 90 days, whereas it was not possible to select replicating virus at TMC114 concentrations above 100 nM even after 260 days. Good correlation was found between the *in vitro* and *in vivo* selected mutations for amprenavir, nelfinavir and lopinavir. Each of the mutations selected *in vitro* with amprenavir (L10F, V32I, L33F, M46I, I47V and I50V) is also selected *in vivo* under amprenavir therapy. *In vivo*, nelfinavir primarily selects D30N, which also appeared first under selection pressure of nelfinavir *in vitro*. Strains that escaped *in vitro* under pressure of lopinavir harboured L10F, M46I, I54V and V82A, also described in patients with viral

rebound during lopinavir/ritonavir therapy. At 100 nM TMC114, viruses harbouring the R41T and K70E mutations were isolated. They all replicated poorly. The virus with the highest fold-change in EC_{50} (FC) for TMC114 (FC=10) showed a FC lower than 10 for the other PIs except for saquinavir (FC=20). The role of the R41T and K70E mutations in decreased susceptibility to TMC114 is under investigation.

CONCLUSION: In a standardized protocol, *in vitro* selection of resistant HIV was much slower with TMC114 as compared to amprenavir, nelfinavir or lopinavir. While virus capable of replicating in micromolar levels of amprenavir, nelfinavir or lopinavir was readily selected, the selection concentration of TMC114 could not be raised above 100 nM. Viruses isolated in the presence of 100 nM TMC114 showed low replication capacity and only a 10-fold change in susceptibility to the inhibitor. Little or no cross-resistance to current PIs, except to saquinavir, was observed with these viruses. These results suggest an increased genetic barrier to the development of resistance to TMC114.

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