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THE PATHWAY LEADING TO TMC114 RESISTANCE IS DIFFERENT FOR TMC114 COMPARED WITH OTHER PROTEASE INHIBITORS

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BACKGROUND: TMC-114 (darunavir), a novel HIV protease inhibitor (PI), is active against wild-type (WT) and PI-resistant HIV-1. *In-vitro* selection experiments from WT HIV-1 were conducted in order to characterize the pathway leading to resistance to TMC-114.

METHODS: HIV-1-infected MT4 cells were exposed to increasing concentrations of TMC-114 and other PIs, to select for viruses able to replicate at high PI concentrations. Phenotypes and genotypes of selected HIV populations were determined by the Antivirogram® and virco®TYPE assays, respectively. Site-directed mutants (SDM) were constructed using the Medigenomix™ proprietary technology.

RESULTS: Data already presented has shown that 75 passages (260 days) of HIV-1/IIIB in the presence of increasing concentrations of up to 200nM TMC-114 resulted in virus populations with the protease mutations R41T and K70E. These viruses showed resistance to TMC-114 (fold change in EC₅₀ [FC] ~10), but replicated poorly. Moreover, SDM strains with these two mutations were not resistant to TMC-114. The study has now been extended to 327 passages (1,155 days), and selected viruses have shown TMC-114 FC >10. Virus populations did not grow at TMC-114 concentrations exceeding 350nM. The H69Q and V77I mutations also accumulated in the protease. Eight mutations in the *gag* gene, both inside and outside the cleavage sites, were also observed. Recombinant viruses encompassing the protease and reverse transcriptase of the selected viruses remained susceptible to TMC-114 (FC<1). Recombinant viruses encompassing *gag* and protease of the selected viruses had TMC-114 FC values between 1 and 10 (further SDM strains with the mutations in the *gag* gene are currently being constructed). Experiments conducted with other WT HIV-1 strains produced comparable results. In contrast,

experiments conducted with other PIs resulted in a more rapid selection of virus populations able to grow at high micromolar PI concentrations; these viruses contained typical PI resistance-associated mutations.

CONCLUSIONS: Selection of TMC-114-resistant HIV-1 from WT strains is slower and more difficult than for other PIs. Characterization of the selected viruses showed that resistance to TMC-114 occurs through a different pathway compared with other PIs.

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19

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