

**POSTER 68****HIV-1 RT MUTANT Q151L HAS A UNIQUE NRTI SUSCEPTIBILITY PROFILE AND SEVERELY REDUCED FITNESS THAT CAN BE PARTIALLY COMPENSATED BY S68N AND L74I**

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**Background:** GS-9148 (phosphonomethoxy-2'-fluoro-2',3'-dideoxydidehydroadenosine) is a structural analog of dAMP that acts as a chain terminating nucleotide HIV-1 reverse transcriptase (RT) inhibitor. The Q151L RT mutation was selected *in vitro* by GS-9148, resulting in reduced susceptibility specifically to GS-9148 and severely decreased viral replication capacity. At high GS-9148 concentrations, Q151L plus S68N, L74I, K70E, and L187F were selected. In this study, we elucidated a role of the S68N, L74I, K70E, and L187F mutations in Q151L viral fitness and drug susceptibilities.

**Methods:** Site-directed mutant recombinants Q151M and Q151L alone and in combination with S68N, L74I, K70E, and L187F were investigated in MT-2 cells using a 5-day susceptibility assay and viral growth competition assays.

**Results:** The Q151L and Q151L+S68N viruses showed 15-fold and 10-fold reduced susceptibility to GS-9148, respectively, were hypersusceptible to tenofovir and zidovudine, and showed no resistance to FTC, d4T or abacavir. Resistance to GS-9148 increased with the accumulation of mutations; the Q151L+L74I, Q151L+L74I+K70E, and Q151L+L74I+K70E+L187F viruses showed 25-fold, >40-fold, and >40-fold resistance to GS-9148, respectively, but were hypersusceptible to tenofovir and zidovudine. In direct fitness competition experiments, all Q151L viruses showed severe fitness defects compared to wild-type or Q151M viruses (1+s values ranging from 0.3 to 0.6). Addition of S68N or L74I to Q151L partially restored the replication defect of the Q151L virus. The mutants Q151L+L74I+K70E and Q151L+L74I+K70E+L187F showed a greater replication defect compared to the Q151L+L74I virus. Overall, the viral fitness was wild-type > Q151M > Q151L+L74I > Q151L+S68N ≈ Q151L+L74I+K70E > Q151L+L74I+K70E+L187F > Q151L.

**Conclusions:** The HIV-1 RT mutant Q151L is highly resistant to GS-9148, has severely decreased viral fitness, and is hypersusceptible to tenofovir and zidovudine. The addition of S68N to the Q151L virus partially compensates for the fitness defect and decreases the resistance to GS-9148. The addition of the L74I, K70E, and L187F mutations to Q151L increases both the fitness of the virus and the resistance to GS-9148. The severely decreased fitness of the Q151L virus and the further development *in vitro* of a complex set of compensatory mutations may present a high *in vivo* resistance barrier for GS-9148.