HIV Resistance to Dolutegravir (DTG) Simultaneously Diminishes Viral DNA Integration into Host Cells and Viral Replication Fitness: Implications for HIV Reservoirs

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Background: No HIV-infected patient, naive to the therapeutic use of integrase strand transfer inhibitors (INSTIs), has yet developed resistance against dolutegravir (DTG). To characterize the resistance profile of DTG, we selected for resistance in tissue culture against this compound.

Methods: We grew HIV-1 of different subtypes in both MT-2 cells and in peripheral blood mononuclear cells over protracted periods, with the concentration of DTG being incrementally increased from 0.05 nM, i.e. 4 times less than the EC50. After a total of 6 months, a final drug concentration of 50-100nM was achieved, beyond which virus could no longer be grown. Viral DNA was sequenced and the biological relevance of any mutations was confirmed biochemically and by site-specific mutagenesis.

Results: R263K or G118R followed by H51Y were the most frequent integrase resistance mutations to arise in subtypes B and C, respectively. R263K alone conferred an approximate 2-5-fold level of resistance to DTG and a 30% drop in levels of recombinant integrase strand transfer activity and viral replicative capacity. Although H51Y alone did not significantly affect either enzyme activity or DTG resistance, the combination of R263K together with H51Y increased DTG resistance to about 12-fold accompanied by a ≈70% loss in each of viral replication capacity, the ability of viral DNA to become integrated into host cell DNA, and integrase strand tranfer activity as measured in biochemical assays using purified integrase enzyme. Over > 1 year, no additional possibly compensatory mutations were identified.

Conclusion: These results stand in contrast to those obtained with other drugs, whereby secondary mutations increase overall levels of drug resistance and simultaneously increase viral replication and enzyme function, and help to explain why primary resistance to DTG has not yet arisen in clinical studies. Validation of these findings in animal models may support the use of DTG in strategies aimed at purging HIV cellular reservoirs, perhaps over several cycles of DTG treatment, if it can indeed be shown that resistance to DTG is not compensated by other mutations located either within the integrase gene or elsewhere in the HIV genome.