

17th International HIV Drug Resistance Workshop



10-14 June 2008, Sitges, Spain

RESISTANCE MUTATIONS IN HIV-1 INTEGRASE SELECTED WITH RALTEGRAVIR OR ELVITEGRAVIR CONFER REDUCED SUSCEPTIBILITY TO A DIVERSE PANEL OF INTEGRASE INHIBITORS

Antivir Ther. 2008; 13(Suppl. 3):A11 (abstract no. 9)

O Goethals, R Clayton, E Wagemans, M Van Ginderen, A Vos, P Geluykens, K Dockx, V Smits, G Meersseman, D Jochmans, S Hallenberger and K Hertogs
Tibotec BVBA, Mechelen, Belgium

BACKGROUND: The first generation integrase inhibitors, raltegravir (RAL, MK-0518) and elvitegravir (ELV, GS-9137) show great promise for the treatment of HIV infection. However, as with all antiretroviral drugs, resistance to integrase inhibitors (INIs) is expected to emerge. Currently, little is known regarding resistance associated mutations (RAMS) to INIs and the degree of cross-resistance conferred by those mutations.

METHODS: We used *in vitro* selection (IVS) with MT4/IIIB to delineate the emergence of RAMS to raltegravir and elvitegravir, conducting eight parallel IVS experiments for each inhibitor. The resulting viruses were genotyped and phenotyped and mutants were generated by site-directed mutagenesis (SDMs) to assess the effect of selected RAMS on the susceptibility to a panel of INIs including raltegravir, elvitegravir, L-870,810, PYRAZ (a pyrimido-azepine), PYCA (a pyrido-carboxamide) and L-731,988.

RESULTS: Population genotyping of viruses selected with raltegravir highlighted one pathway towards resistance, that is, Q148R followed by E138K, G140A and V54I. One selected virus (genotype Q148R, E138K, G140A and V54I) showed greatly reduced susceptibility for both raltegravir and elvitegravir (>600-fold) and significantly reduced susceptibility to other INIs. An SDM carrying the Q148R mutation alone showed reduced susceptibility to raltegravir (22-fold) and elvitegravir (47-fold). Combined mutations Q148R and G140A further reduced susceptibility to raltegravir (>1,000-fold) and elvitegravir (260fold). Resistant viruses selected with elvitegravir contained at least one of the following RAMS: Q148R, E92Q and T66I in addition to further mutations (H114Y, L74M, R20K, A128T, E138K and/or S230R). All selected viruses showed significantly reduced susceptibility to elvitegravir and other INIs with only moderately reduced susceptibility to raltegravir. The SDMs E92Q and T66I were

significantly reduced in susceptibility to elvitegravir (57-fold and 35-fold, respectively) with small reductions in susceptibility to raltegravir.

CONCLUSIONS: The Q148R mutation is selected by both raltegravir and elvitegravir and conferred resistance to a diverse panel of INIs. Additionally, mutations selected with elvitegravir (E92Q and T66I) conferred significant resistance to many INIs with a small reduction in susceptibility to raltegravir. We suggest that Q148R, E92Q and T66I be considered as RAMS conferring resistance to a diverse panel of INIs.

2008-06-10

9

Copyright © 2008 - [International Medical Press Ltd.](#). Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.