Retrovirology



Poster presentation



# G140S mutation rescues HIV-1 IN integration defect due to Q148H *in vitro* and *in vivo*

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Raltegravir (MK-0518) is clinically used against viruses resistant to other antiretroviral compounds. However, it has been reported that Raltegravir induces integrase (IN) resistance very soon after the administration of the drug. Some residues in the protein seem to be preferentially targeted: E92Q, N155H, and the double mutant G140S/Q148H. It was demonstrated that most of these mutations altered both 3'-processing and strand transfer activities of IN. In this report, we addressed for the first time by real time PCR the kinetics of the integrase mutants as well their resistance towards Raltegravir. Furthermore, we characterised the activities of the recombinant proteins. Our data highly suggest that the resistance towards Raltegravir is due to the mutation Q148H. This mutation results in a slower replication kinetic which is compensate by the G140S mutation. These data explain why only the double mutant G140S/Q148H is observed in clinical trials as one of the most prevalent profile of raltegravir resistance.

Two patients receiving raltegravir as part as their regimen were followed. After a viral load decrease, these patients harbored virological failure and selection of raltegravir resistance mutations in the integrase gene (N155H for patient 1 and G140S + Q148H for patient 2). At failure, patients harbouring viruses with these raltegravir mutations showed HIV viral load rebound corresponding to baseline values.

## Methods

The two most prevalent profiles of raltegravir mutations were studied (N155H and G140S + Q148H). Recombinant viruses harbouring the mutations N155H, E92Q, G140S/Q148H were constructed by site directed mutagenesis. To study the influence of each mutation on the residues G140 and Q148, viruses harbouring these mutations were constructed. All these mutations were also introduced in a plasmid encoding proteins in order to obtain recombinant mutated IN.