Secondary resistance mutations in the R263K integrase inhibitor resistance pathway

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Introduction

HIV-1 resistance has been observed for all antiretrovirals tested so far, raising concerns about the long-term efficacy of these drugs. However, no resistance mutation against the strand-transfer inhibitor dolutegravir has been observed in treatment-naïve patients. In *in vitro* selection studies performed in our laboratory demonstrated that, in the presence of dolutegravir, the R263K mutation commonly emerges in integrase and is often associated with the secondary mutation H51Y. We have shown that R263K confers resistance to dolutegravir while the addition of H51Y to R263K further decreases HIV susceptibility to this drug. However, resistance correlated with a pronounced decrease in integration and viral replication. Although less common than H51Y, other secondary mutations such as M50I and E138K were selected in the presence of the R263K primary mutation.

HIV infectivity in the presence of the R263K and H51Y/R263K mutations

E138K fails to compensate for the R263K resistance mutation

E138K does not R263K defect in HIV infectivity and replication

E138K modestly increases resistance against dolutegravir conferred by the R263K mutation

Localisation of R263K and E138K by homology modeling

Defects in viral replication caused by the R263K resistance pathway impairs the ability of HIV to acquire resistance against nevirapine and lamivudine

Nevirapine in *in vitro* selection

Lamivudine in *in vitro* selection

Conclusion

So far, no secondary mutation has been shown to compensate for the defects associated with the R263K primary resistance mutation against dolutegravir. All secondary mutations have a modest effect on resistance against this drug. These results may provide an explanation for the absence of de novo resistance mutations against dolutegravir in naïve patients. Additionally, the presence of the R263K and H51Y/R263K mutations impairs the ability of HIV to acquire further resistance against some RT inhibitors.

References


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