Characterization of a G118R plus R263K combination of integrase resistance mutations associated with HIV viral load rebound in a patient failing dolutegravir-based therapy

Jewish General Hospital
Lady Davis Institute

Meng Xiao, Jenna Cleyle, Sunbin Yoo, Mekayla Forrest, Hanh Thi Pham, and Thibault Mesplède

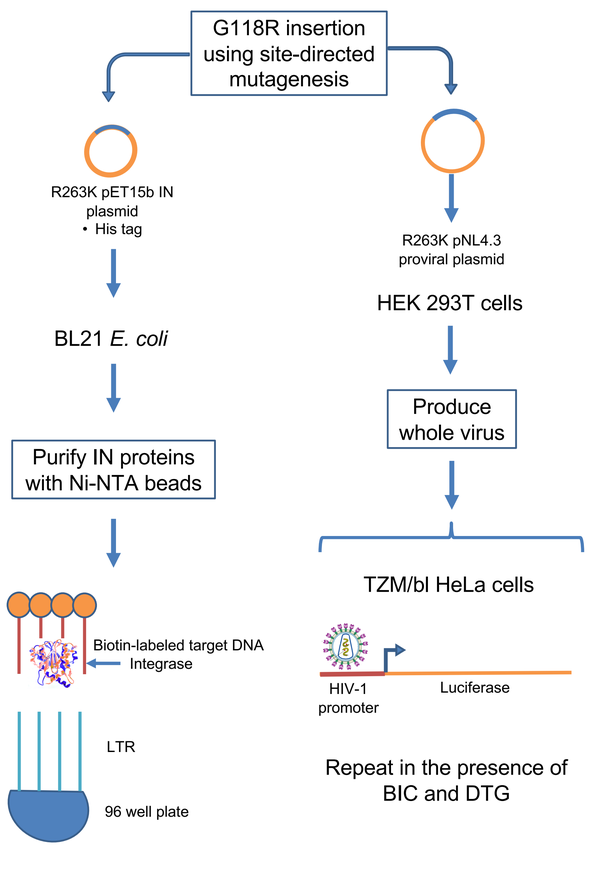
McGill AIDS Centre, Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, QC, Canada
Department of Microbiology and Immunology, Faculty of Medicine, McGill University, Montréal, Québec, Canada

McGill University

Scientific background

Integrase inhibitors are antiretroviral drugs boasting high potency and tolerability. Among those, dolutegravir (DTG) and bictegravir (BIC) also have high genetic barriers to resistance. HIV resistance mutations have the potential to jeopardize the efficacy of antiretroviral therapy, increasing the likelihood of a viral rebound in patients. The DAWNING clinical trial demonstrated the superiority of DTG to r/LPV when either was combined with 2 NRTIs in treatment-experienced individuals for 48 weeks. One patient who experienced treatment failure in the DTG arm of this trial was found to live with a virus that bore the G118R and R263K integrase substitutions in combination. This combination was not previously described. Here, we characterized the effects of the G118R/R263K combination of integrase substitutions on transfer activity, viral infectivity, and susceptibility to the integrase inhibitors DTG and BIC, since the latter may be considered as a treatment option following failure with the former.

Experimental approach



Results

1. G118R/R263K reduces integrase strand transfer activity

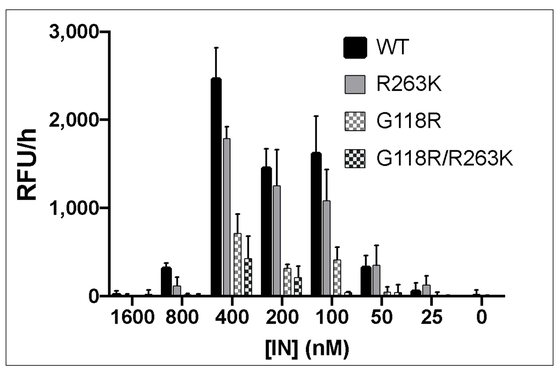


Figure 1. Strand transfer with various concentrations of recombinant integrase proteins

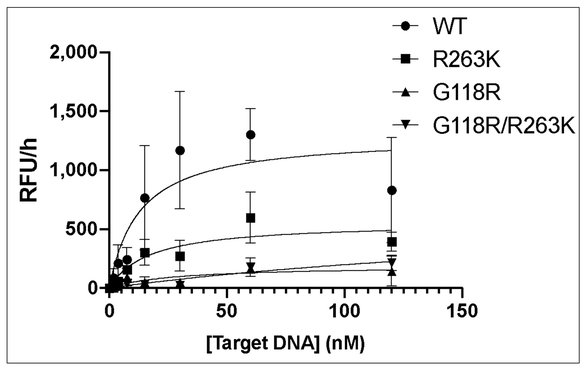


Figure 2. Strand transfer activity of recombinant integrase proteins in presence of various concentrations of target DNA

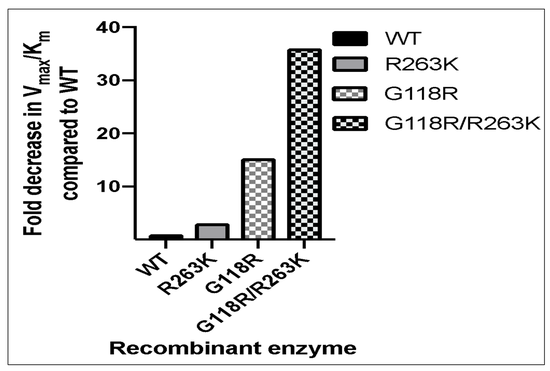


Figure 3. Fold change in strand transfer efficiency of integrase proteins compared to wild type

2. G118R/R263K diminishes viral infectivity

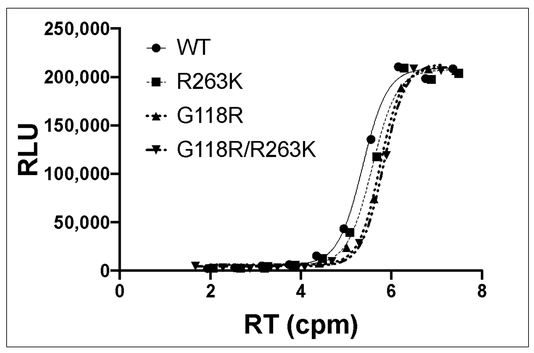


Figure 4. Relative infectivity of WT, R263K, G118R, and G118R/R263K viruses.

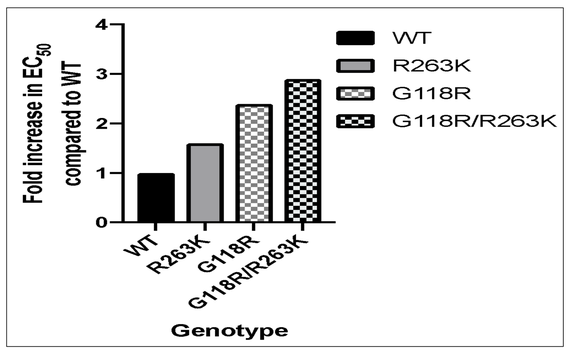


Figure 5. Fold change in EC_{50} of R263K, G118R, and G118R/R263K viruses compared to wild type

3. G118R/R263K virus is highly resistant to dolutegravir and bictegravir

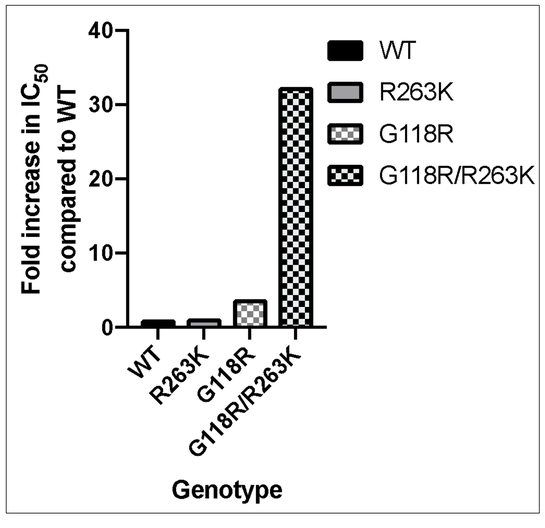


Figure 6. Fold change in IC50 of R263K, G118R, and G118R/R263K viruses in the presence of BIC compared to wild type

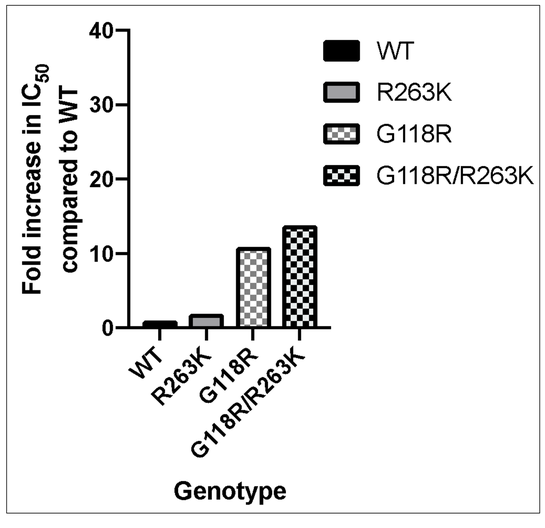


Figure 7. Fold change in IC50 of R263K, G118R, and G118R/R263K viruses in the presence of DTG compared to wild type

Conclusions

Our results show that the G118R/R263K substitutions in combination result in decreased strand transfer efficiency, lower viral infectivity, and increased resistance to both DTG and BIC compared to the single mutants and wild type virus. From our results, we conclude that BIC should not be considered following DTG failure with the G118R plus R263K combination of mutations.

Future Directions

It would be valuable to perform selection studies with BIC to determine if the G118R/R263K combination can emerge only in DTG-based treatments, or if it can also arise upon treatment with other integrase inhibitors. This question is especially important given the significant increase in drug resistance that the G118R/R263K virus displayed against BIC. Further characterization of the drug resistance profile of this virus to other integrase inhibitors is also required, particularly given the potential for cross-resistance to multiple drugs.

Conflict of Interest Disclosure: We have no conflict of interest in relation to this work.