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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Introduction

- HIV-1 resistance has been observed for all antiretrovirals tested so far.
- No resistance mutation against the second generation strand-transfer inhibitor dolutegravir has been observed in treatment-naïve patients.

Results

- In vitro selection studies performed in our laboratory demonstrated that, in the presence of dolutegravir the R263K mutation commonly emerges in integrase.

**Primary resistance mutation in integrase selected with dolutegravir in cell culture:**

R263K

- R263K confers low-level resistance against dolutegravir and diminishes HIV DNA integration and viral fitness.

<table>
<thead>
<tr>
<th>Genotype (DTG)</th>
<th>Resistance</th>
<th>Integration</th>
<th>Viral replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>R263K</td>
<td></td>
<td>≈80 %</td>
<td>≈80 %</td>
</tr>
<tr>
<td>WT</td>
<td>-</td>
<td>100 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>

- R263K can associates with several secondary mutations of which the most common is HS1Y. R263K is also associated with the polymorphism M50I and another secondary mutation: E138K.

**In vitro selection (Time)**

WT → R263K → R263K/HS1Y → R263K/M50I → R263K/E138K

- The addition of HS1Y to R263K further increases HIV resistance against dolutegravir but this correlates with a decrease in integration and viral replication.

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</thead>
<tbody>
<tr>
<td>R263K</td>
<td></td>
<td>≈60 %</td>
<td>≈40 %</td>
</tr>
<tr>
<td>WT</td>
<td>-</td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>R263K</td>
<td>+</td>
<td>≈80 %</td>
<td>≈80 %</td>
</tr>
<tr>
<td>R263K/HS1Y</td>
<td>+</td>
<td>≈60 %</td>
<td>≈40 %</td>
</tr>
</tbody>
</table>

- Similar results are observed with M50I and E138K: both fail to restore HIV viral replication capacity and integration defect caused by R263K.

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 INI-naïve patients.

Summary

In this illustration, dolutegravir (DTG) is used to treat an individual (Leonardo da Vinci) living with HIV (in red). By far the most common first mutation that could emerge against dolutegravir is R263K. However, no secondary mutation compensate for the defects in viral replication and integration caused by R263K. Therefore, the virus is trapped in an evolutionary dead-end.

Acknowledgments

This project was supported by the Canadian Institutes for Health Research (CIHR), the Canadian Foundation for AIDS Research (CanFAR) and ISTP Canada. Dr. Thibault Mesplède is the recipient of the Bristol-Myers Squibb/CIHR Canadian HIV Trials Network (BMS/CTN) postdoctoral fellowship.

References