Drug Resistance to Integrase Strand Transfer Inhibitors in HIV-1 Chilean Patients. Frequency and evolution between the years 2013 and 2016.

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Disclosure

• Nothing to disclosure
Introduction

- The integrase strand transfer inhibitors (INSTIs) are safe and effective drugs for the treatment of the HIV-1.

- Raltegravir (RAL, FDA 2007) and Elvitegravir (EVG, FDA 2012 belongs to the 1st generation INSTIs and Dolutegravir (DTG, FDA 2013), to the 2nd generation.

- All of them are available in Chile. RAL was the first drug introduced in the country on 2008; until December of 2016 was the only one available in the public health system.
Integrase strand transfer inhibitors (INSTIs)

- They block the viral DNA integration to the cell genoma, leading to the strand transfer process inhibition.
Raltegravir’s Resistance

- There are three resistance pathways:
  - N155H
  - Q148H/K/R
  - Y143R/H/C (RAL’s exclusive)

- Secondary mutations lead to increased resistance: L74M, E92Q, T97A, E138A/K, G140A/S

- There’s low Transmitted Drug Resistance TDR (< 1%)
# Major Primary INSTI Resistance Mutations

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>E</th>
<th>E</th>
<th>G</th>
<th>Y</th>
<th>Q</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raltegravir</strong></td>
<td>66</td>
<td>92</td>
<td>138</td>
<td>140</td>
<td>143</td>
<td>148</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Q</td>
<td>KA</td>
<td>SA</td>
<td>RCH</td>
<td>HRK</td>
<td>H</td>
</tr>
<tr>
<td><strong>Elvitegravir</strong></td>
<td>66</td>
<td>92</td>
<td>138</td>
<td>140</td>
<td>147</td>
<td>148</td>
<td>155</td>
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<tr>
<td></td>
<td>IAK</td>
<td>Q</td>
<td>KA</td>
<td>SA</td>
<td>G</td>
<td>HRK</td>
<td>H</td>
</tr>
<tr>
<td><strong>Dolutegravir</strong></td>
<td>92</td>
<td>138</td>
<td>140</td>
<td>148</td>
<td>263</td>
<td>148</td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>Q</td>
<td>KA</td>
<td>SA</td>
<td>HRK</td>
<td>K</td>
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</tr>
</tbody>
</table>

Mutations in **ORANGE** associated with highest levels of reduced susceptibility or response.

Mutations in **YELLOW** reduce INSTI susceptibility or response.

Adapted from the Stanford HIV Drug Resistance Database.
The 1st Generation INSTIs have a low genetic barrier but a high “robustness”.

There is a low risk to develop resistance if the drug is part of a full score treatment of three drugs and the patient has good adherence.

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>E</th>
<th>G</th>
<th>Q</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravinir</td>
<td>92</td>
<td>138</td>
<td>140</td>
<td>148</td>
<td>263</td>
</tr>
</tbody>
</table>

Mutations in **ORANGE** associated with highest levels of reduced susceptibility or response.

Mutations in **YELLOW** reduce INSTI susceptibility or response.

Adapted from the Stanford HIV Drug Resistance Database.
INSTIs’s Resistance Mutations

- Resistance mutations in patients with virologic failures (VF) exposed to RAL or EVG, could affect DTG effectiveness.

- In order to have an effective ART it’s very important to detect resistance mutations in patients with VF.

- Jiangzhou You et cols (2016):
  - RAL’s resistance rate: RCT 3.9%.
  - RAL’s resistance rate was higher than EVG y DTG.
  - The 10 most frequent mutations related to the developing on resistance were: N155H, Y143C/R, Q148H/R, Y143Y/H, L74L/M, E92Q, E138E/A, Y143C, Q148Q y Y143S
Objectives

General:
- To determine the INSTI’s resistance pattern in HIV-1 infected patients with virologic failure with ART including INSTIs, treated in Chile between 2013 and 2016.

Specific:
- To evaluate the rate of resistance in patients infected with HIV-1 in ART with INSTIs in virological failure in the long term, treated in Chile between 2013 and 2016.
- To describe the most common resistance-associated mutations in patients infected with HIV-1 in ART with INSTIs in virological failure, treated in Chile between 2013 and 2016.
Materials and Methods

• Observational, longitudinal and descriptive study.

• All patients who had been tested at the Molecular Medicine Laboratory of the HIV Clinic Hospital of the University of Chile (HCUCH) between January 2013 and December 2016, who were being treated with INSTIs in Chile were included.
Materials and Methods

• The resistance genotype was determined by a RT PCR method followed by an automatic sequentiation using Recall™.

• Only the approved sequences were used to obtain a resistance report from the Stanford’s University Database or the Geno2pheno® System.

• “Resistance” was considered when the mutations conferred low, middle or high drug resistance.
Materials and Methods

• The rate of resistance detection was calculated by percentages and their variation in the long term was compared.

• The statistical significance of the variation in the long term was calculated by the Pearson's chi-square test.
Outcomes

Requested and reported tests between 2013 to 2016

<table>
<thead>
<tr>
<th>Year</th>
<th>Requested Tests</th>
<th>Reported Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>2014</td>
<td>197</td>
<td>175</td>
</tr>
<tr>
<td>2015</td>
<td>238</td>
<td>194</td>
</tr>
<tr>
<td>2016</td>
<td>235</td>
<td>178</td>
</tr>
<tr>
<td>2013-2016</td>
<td>711</td>
<td>581</td>
</tr>
</tbody>
</table>

Any INSTI's Resistance’s Rate between 2013 to 2016.

- 2013: 38.2% (13)
- 2014: 24.5% (43)
- 2015: 27.3% (53)
- 2016: 21.9% (39)
- Total: 25.4% (148)

Number and Percentage of Patients with Resistance

p 0.21
Outcomes

Each INSTIs’s resistance rate by year between 2013 to 2016

<table>
<thead>
<tr>
<th>Año</th>
<th>Raltegravir</th>
<th>Elvitegravir</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>38.2%</td>
<td>29.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>2014</td>
<td>21.1%</td>
<td>15.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>2015</td>
<td>25.3%</td>
<td>19.6%</td>
<td>9.8%</td>
</tr>
<tr>
<td>2016</td>
<td>23.8%</td>
<td>19.7%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Total</td>
<td>21.9%</td>
<td>18.9%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

p = 0.16

p = 0.26

p = 0.55
Outcomes

Chile: 32,000 patients receiving HAART

Estimated resistance rate against INTIs in patients receiving ART including RAL in Chile: 3.6%

- Resistencia Estimada = 213
- Fallo Virológico Estimado = 1016
- RAL = 5900
Outcomes

Most frequent mutations detected between 2013 to 2016

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage of total mutations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T97A</td>
<td>7.8</td>
</tr>
<tr>
<td>N155H</td>
<td>7.5</td>
</tr>
<tr>
<td>S119P</td>
<td>6.9</td>
</tr>
<tr>
<td>L74I</td>
<td>6.2</td>
</tr>
<tr>
<td>G140S</td>
<td>5.6</td>
</tr>
<tr>
<td>T124A</td>
<td>5.6</td>
</tr>
<tr>
<td>G163R</td>
<td>5.6</td>
</tr>
<tr>
<td>V120I</td>
<td>4.7</td>
</tr>
<tr>
<td>Q148H</td>
<td>4.7</td>
</tr>
<tr>
<td>V151I</td>
<td>4.4</td>
</tr>
</tbody>
</table>
Outcomes

Major mutations detection’s rate in reported tests.
2013-2016

Percentage of total processed samples

- N155H: 16.2%
- G140A/S: 14.2%
- Q148H/K/R: 14.2%
- Y143R/H/C: 8.8%
- T66I/A/K2: 0.68%
- E92Q: 0.68%
- R263K: 0.00%
Conclusions

• The resistance detection for INSTI’s between 2013 – 2015, at the Molecular Medicine Laboratory from HCUCH, has demonstrated that resistance rates have demonstrated to be stable.

• These rates have not changed in the long term for each INSTI by itself.

• The RAL’s resistance was similar to the reported in others internationals studies.
Conclusions

• At least 40 integrase associated mutations to resistance have been described in the literature. It was shown 2 of them in the 10 most frequent at this study: N155H and Q148H/R

• This study demonstrates that we need to study integrase resistance in patients with VF when there’s an INSTI in the ART as in other internationals recommendations.
Thanks for your attention