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 disclousure

Introduction

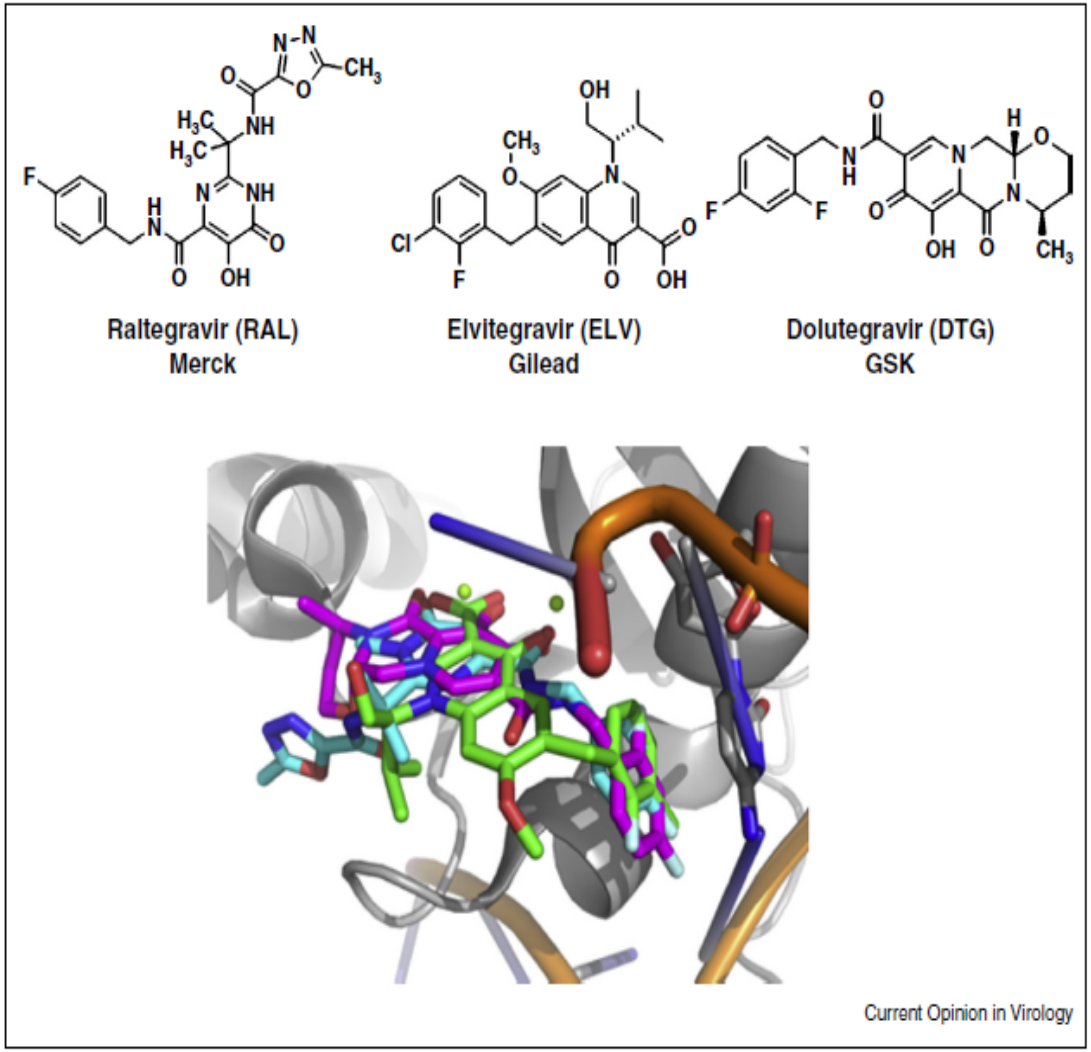
- The integrase strand transfer inhibitors (INSTIs) are safe and effective drugs for the treatment of the HIV-1.

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

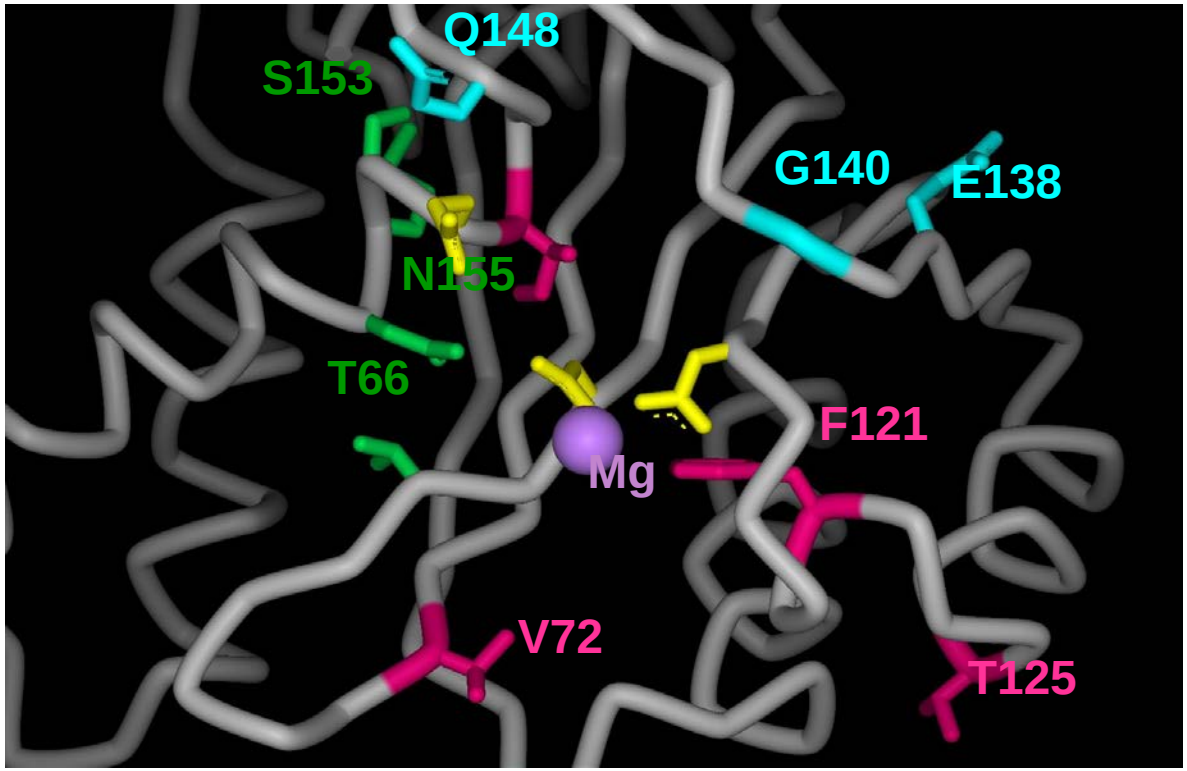
- All of them are available in Chile. RAL was the first drug introduced in the country on 2008; until December of 2016 was the only one available in the public health system.

Integrase strand transfer inhibitors (INSTIs)

- They block the viral DNA integration to the cell genoma, leading to the strand transfer proces inhibition.



INSTIs's Resistance Mutations



- Catalytic residues
- Diketoacid
- Naphthyridine
- Pyrimidine

Hazuda DJ, et al. HIV Resistance Workshop 2007. Abstract 8. Adapted from Merck & Co., Inc., Whitehouse Station, New Jersey, USA. Copyright © 2007 Merck & Co., Inc., Whitehouse Station, NJ, USA. All rights reserved.

Raltegravir's Resistance

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

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

- There's low Transmited Drug Resistance TDR (< 1%)

Major Primary INSTI Resistance Mutations

	T	E	E	G	Y		Q	N	
Raltegravir	66	92	138	140	143		148	155	
	A	Q	KA	SA	RCH		HRK	H	
	T	E	E	G		S	Q	N	
Elvitegravir	66	92	138	140		147	148	155	
	IAK	Q	KA	SA		G	HRK	H	
		E	E	G			Q		R
Dolutegravir		92	138	140			148		263
		Q	KA	SA			HRK		K

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.

Major Primary INSTI Resistance Mutations

The 1st Generation INSTIs have a low genetic barrier but a high "robustness".

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

	E	E	G	Q	R
Dolutegravir	92	138	140	148	263
	Q	KA	SA	HRK	K

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 determinated by a RT PCR method followed by an automatic secuentiation using RecalI™.

- Only the approved secuences 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.

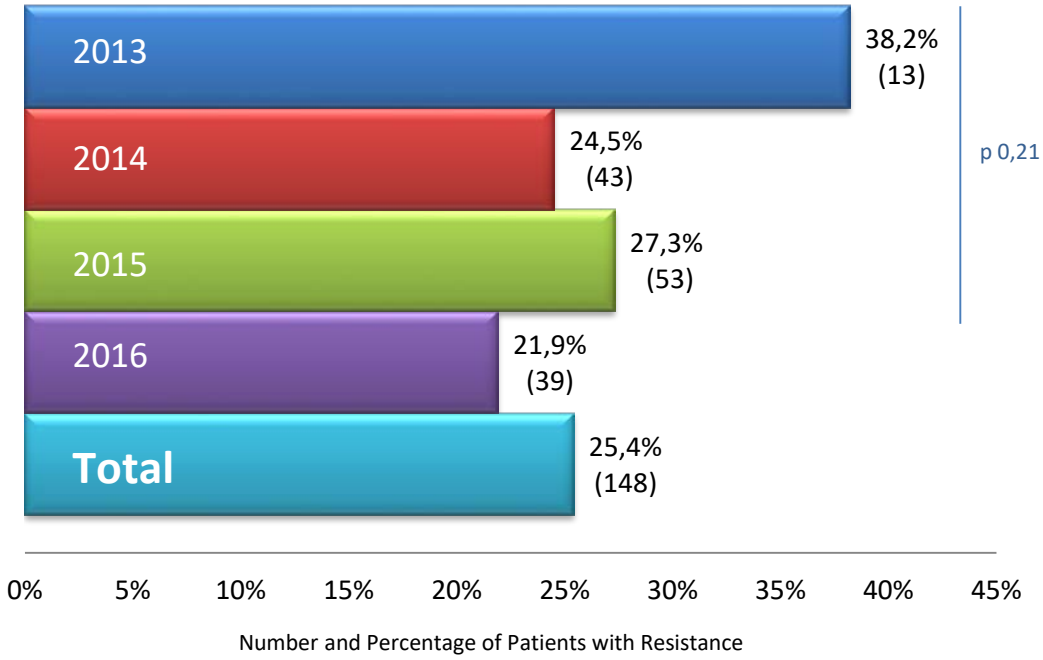
- The statistical significance of the variation in the long term was calculated by the Pearson's chi-square test

Outcomes

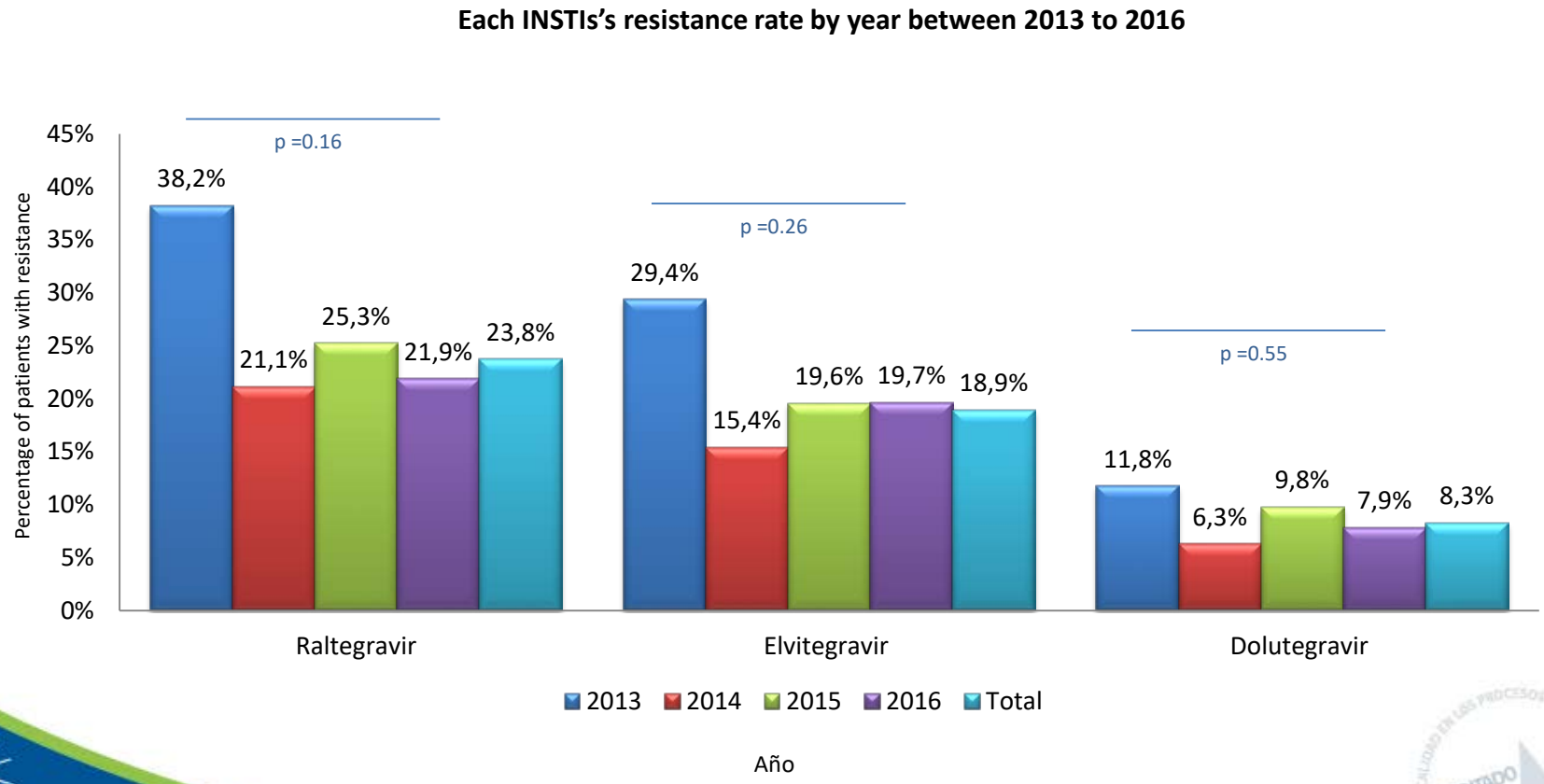
Requested and reported tests between 2013 to 2016

Year	Requested Tests	Reported Tests
2013	41	34
2014	197	175
2015	238	194
2016	235	178
2013-2016	711	581

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

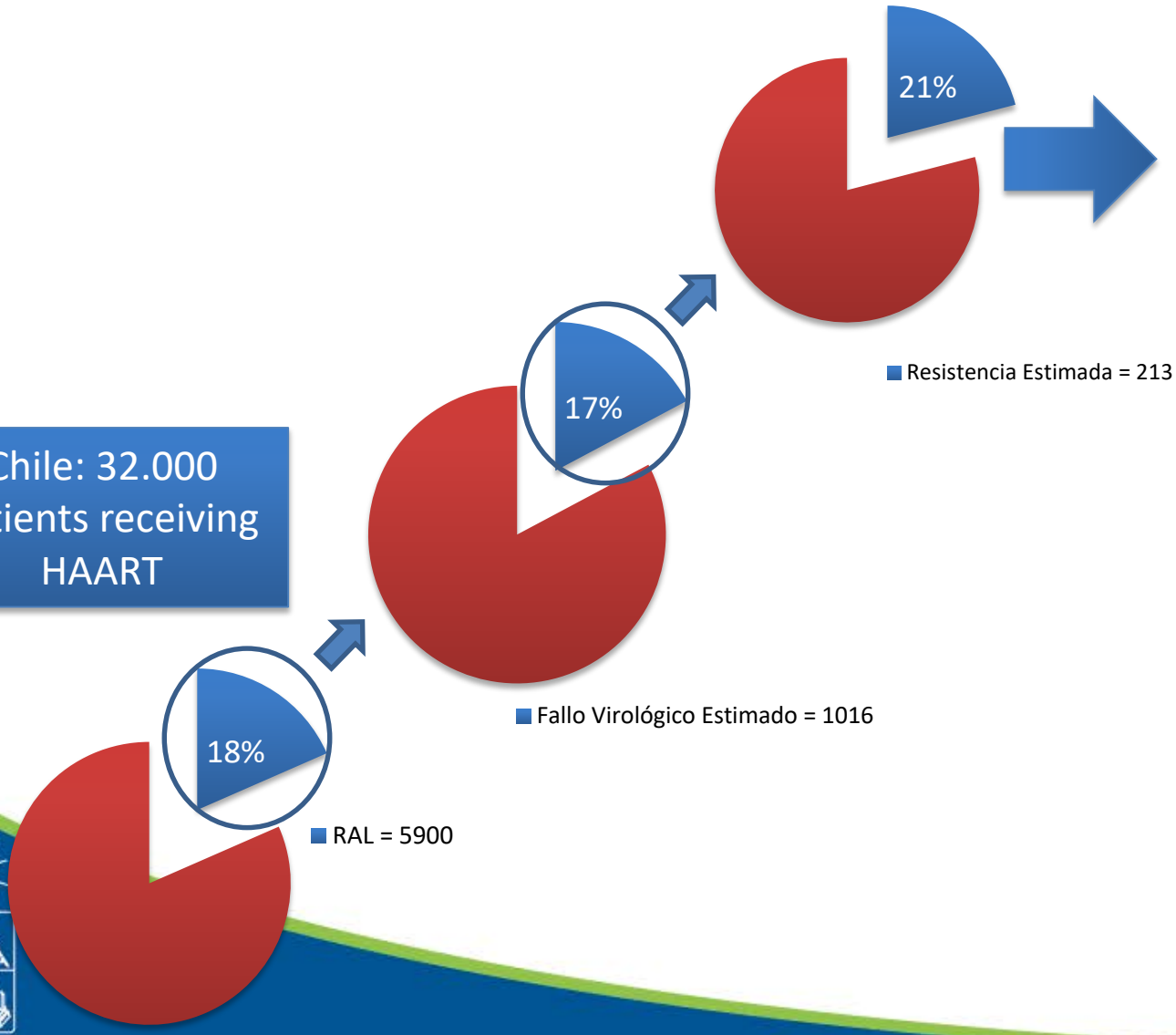


Outcomes


Each INSTIs's resistance rate by year between 2013 to 2016
Percentage of patients with resistance
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
p =0.16
p =0.26
p =0.55
38,2%
21,1%
25,3%
21,9%
23,8%
29,4%
15,4%
19,6%
19,7%
18,9%
11,8%
6,3%
9,8%
7,9%
8,3%
Raltegravir
Elvitegravir
Dolutegravir
2013
2014
2015
2016
Total
Año

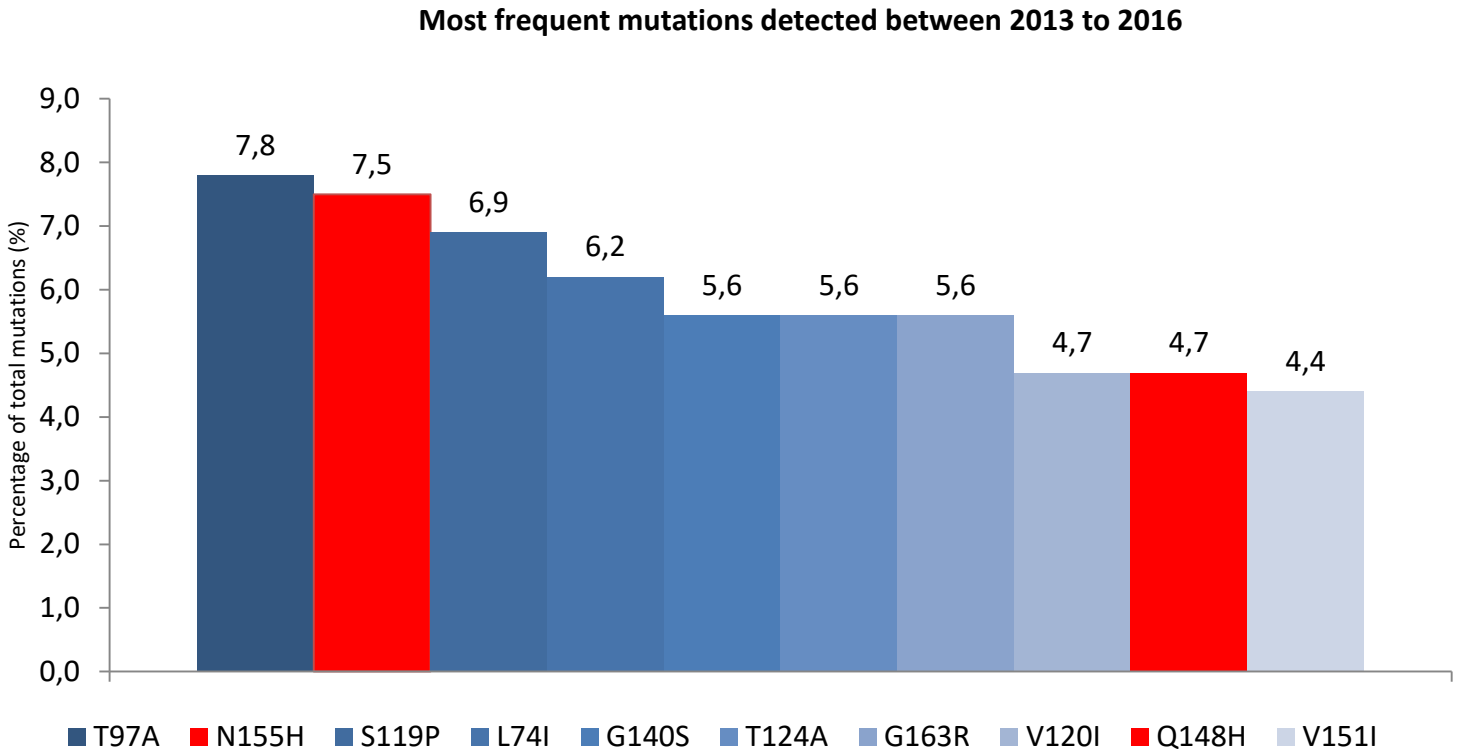
Outcomes

Chile: 32.000 patients receiving HAART

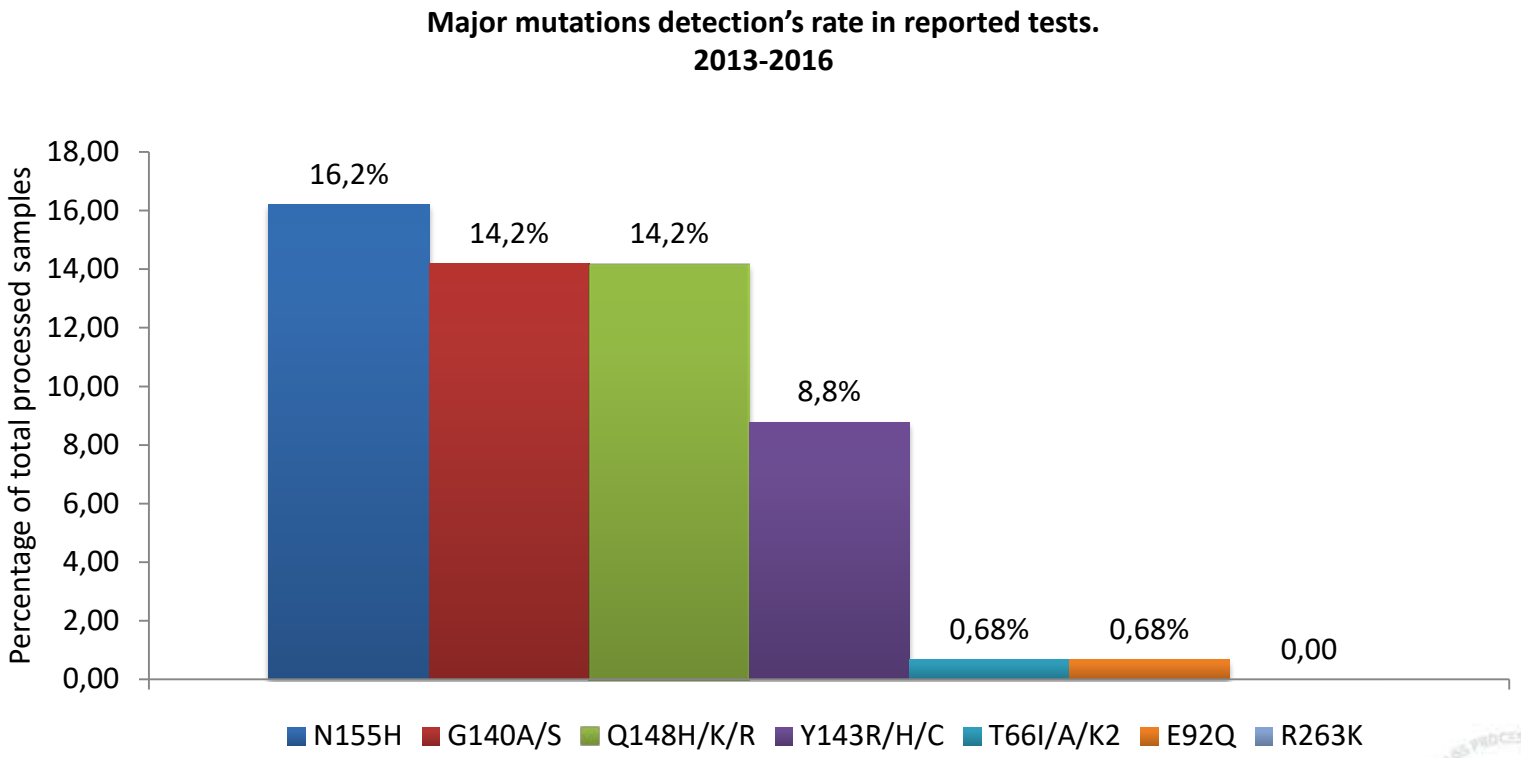


Estimated resistance rate against INTIs in patients receiving ART including RAL in Chile: 3,6%

Outcomes



Outcomes


Major mutations detection's rate in reported tests.
2013-2016
Percentage of total processed samples
18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
16,2%
14,2%
14,2%
8,8%
0,68%
0,68%
0,00
N155H
G140A/S
Q148H/K/R
Y143R/H/C
T66I/A/K2
E92Q
R263K

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 asociated 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