

# Prevalence of Integrase Inhibitor Resistance Mutation in patients with therapeutic failure

Viciano I<sup>1,2</sup>, García Pérez<sup>2</sup>, González-Domenech CM<sup>3</sup>, Gómez-Ayerbe C<sup>1,2</sup>, Bardón P<sup>2</sup>, Palacios R<sup>1,2</sup>, Castaño M<sup>4</sup>, del Arco A<sup>5</sup>, Téllez F<sup>6</sup>, Clavijo E<sup>2</sup>, Santos J<sup>1,2</sup>

<sup>1</sup>Institute of Biomedical Investigation of Malaga (IBIMA), Spain; <sup>2</sup>Hospital Virgen de la Victoria, UGC Infectious Diseases and Microbiology, Malaga, Spain; <sup>3</sup>Department of Microbiology, University of Granada; <sup>4</sup>Hospital Regional Carlos Haya, UGC Infectious Diseases and Microbiology, Malaga, Spain; <sup>5</sup>Hospital Costa del Sol UGC Infectious Diseases and Microbiology, Malaga, Spain; <sup>6</sup>Hospital Puerto Real UGC Infectious Diseases and Microbiology Cádiz, Spain.



UNIVERSIDAD DE GRANADA



## Background

First-generation Integrase Inhibitors (INI), Raltegravir (RTG) and Elvitegravir (EVG) have a low genetic barrier and broad cross-resistance among them. Dolutegravir (DTG) has a higher genetic barrier and isolates resistant to RTG and EVG remains sensitive to it. The aim of this study was to identify the most frequent resistance mutations patterns selected at the virological failure with a regimen including INI, as well as the susceptibility to the drugs of this family

## Material and Methods

- We considered all the HIV-1 integrase genotype resistance tests performed to patients with virological failure with a regimen with INI, at Virgen de la Victoria Hospital, reference center in southern Spain, from 2012 to 2018.
- Drug resistance mutations were determined with Viroseq® HIV Integrase system
- The resistance mutations were predicted using Stanford algorithm v7.1.1.
- We also collected demographic, clinical and immunovirological data.

## Results

Table 1. Characteristics of the patients with virological failure with a regimen with INI

Characteristics			
Number of patients		236	
Age (years)		49	IQR: 16-72
Viral load		3.34	IQR: 2.01-6.22
Lymphocyte CD4 count		363	IQR: 6-1926
Sex	Male	176	74.6%
	Female	60	25.4%
Subtype	B	199	84.3%
	No B	37	15.7%
Treatment	RTG	138	58.5%
	EVG	35	15.7%
	DTG	61	25.8%
Failure	First	68	28.8%
	Two/more	151	64%
	Discontinued	17	7.2%
Patients with mutations		64	27%

Viral load is expressed in log copies/mL and the CD4 count in cells/ $\mu$ L. The quantitative variables are expressed as median and IQR or mean and the qualitative variables as n (%).

Table 2. Patients with selected mutations at virological failure with a regimen with INI

Failure	Mutations	N	%
First (68)	No	52	75%
	Yes	16	25%
Two/more (151)	No	104	68.9%
	Yes	47	31.1%
Discontinued (17)	No	16	94.1%
	Yes	1	5.9%

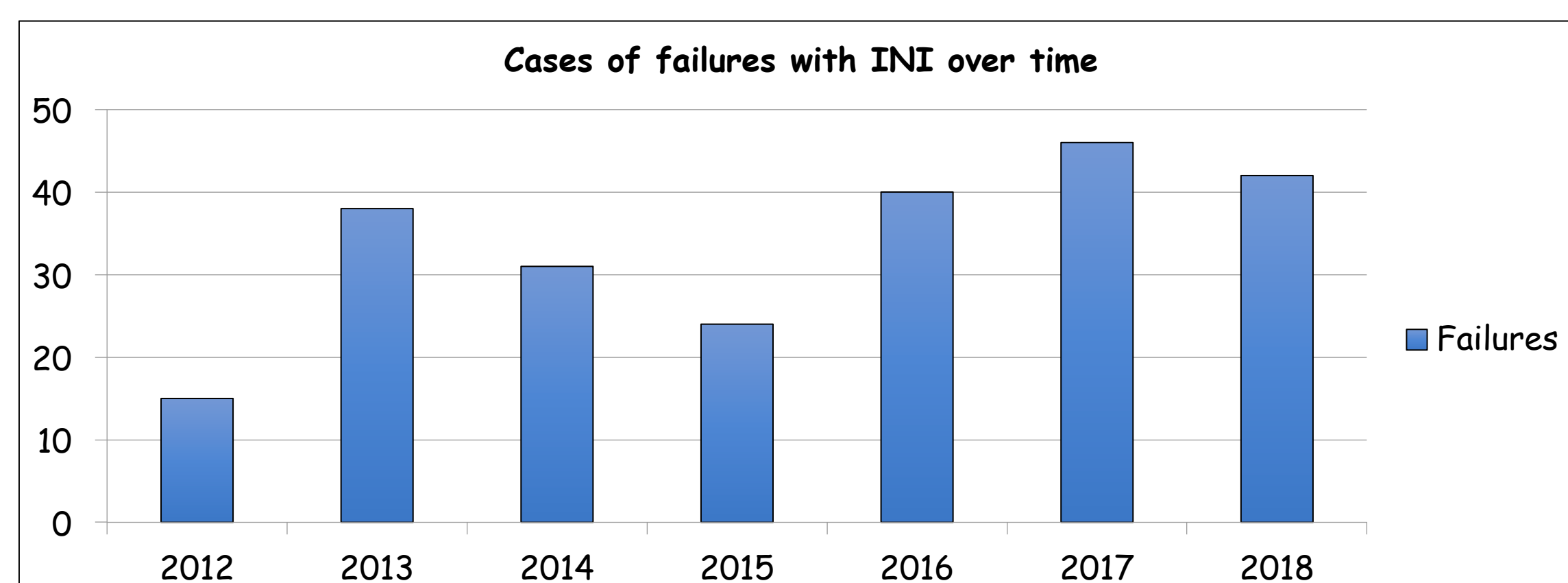


Fig.1. Cases of failures with INI in our area over time

## Conclusions

1. Over a quarter of patients in VF selected resistance mutations to integrase.
2. The most frequently mutations selected were 140ACS+148H, 92Q+97A, and 263K plus other mutations for patients treated with RTG, EVG and DTG respectively.
3. Almost three out of four patients presented resistance to RTG and EVG whereas resistance to DTG did not reach ten percent.
4. DTG continues maintaining activity against many of the isolates resistant to first generation INI.

Table 3. Characteristics of the patients with virological failure with a regimen with RTG

Characteristics		Cohort with a regimen with RTG	
Number of patients		138	
Age (years)		49	IQR: 16-53
Viral load		3.34	IQR: 2.01-6.22
Lymphocyte CD4 count		363	IQR: 6-1926
Sex	Male	101	73.2%
	Female	37	26.8%
Subtype	B	118	85.5%
	No B	20	14.5%
Failure	First	27	19.6%
	Two/more	104	75.4%
	Discontinued	7	5.1%
Patients with mutations		43	31.2%
Most frequent pattern	140ACS+148H	7	5.1%
	138K+148H	4	2.8%
	155H+other	15	5.1%
	143HCR+other	6	4.3%
	Other mutations	11	7.9%

Table 4. Characteristics of the patients with virological failure with a regimen with EVG

Characteristics		Cohort with a regimen with EVG	
Number of patients		37	
Age (years)		45	IQR: 15-55
Viral load		3.72	IQR: 2.04-6
Lymphocyte CD4 count		336	IQR: 6-1673
Sex	Male	33	89.2%
	Female	4	10.8%
Subtype	B	30	81.1%
	No B	7	14.5%
Failure	First	21	56.8%
	Two/more	13	37.8%
	Discontinued	3	8.1%
Patients with mutations		12	32.4%
Most frequent pattern	92Q+97A	4	10.8%
	92Q+other	4	10.8%
	155H+other	2	5.4%
	148H	1	2.7%
	Other mutations	1	2.7%

Table 5. Characteristics of the patients with virological failure with a regimen with DTG

Characteristics		Cohort with a regimen with DTG	
Number of patients		61	
Age (years)		51	IQR: 25-63
Viral load		3.15	IQR: 2.03-6.5.64
Lymphocyte CD4 count		363	IQR: 7-1516
Sex	Male	42	68.9%
	Female	19	31.1%
Subtype	B	51	83.6%
	No B	10	16.4%
Failure	First	20	32.8%
	Two/more	34	55.7%
	Discontinued	7	11.5%
Patients with mutations		9	14.7%
Most frequent pattern	263K+other	3	5.1%
	138K+148H	2	2.8%
	155H	1	5.1%
	138K	1	4.3%
	Other mutations	2	7.9%

Table 6. Drug Resistance Interpretation to INI

	Susceptible	Intermediate Resistance	High Level Resistance
RALTEGRAVIR	75.4%	4.7%	19.9%
ELVITEGRAVIR	76.7%	2.5%	20.8%
DOLUTEGRAVIR	91.5%	2.5%	5.9%