Resistance to second-Generation InSTIs in Mexican PLWH: Emergence of the R263K Mutant

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Resistance to 2nd generation integrase inhibitors is a rare phenomenon even in places where the use of these drugs is extensive.
In the limited number of samples with resistance to these drugs mutant R263K is increasing its detection frequency.
The presence of the combination of mutants R263K and M50I is related to long time in virological failure and to low viral loads probably associated to a fitness effect.

BACKGROUND

- Clinical trials and real–life experience have shown limited resistance development after use of second generation INSTIs, specially in first line. One of the mutants found in this scenario is the R263K, a nonpolymorphic mutation that alone reduces DTG, BIC, and CAB susceptibility about 2–fold. This mutation has been described in first line failure to second generation InSTIs.

METHODS

- We analyzed all the samples submitted for integrase resistance genotype (Abbot ViroSeq HIV 1Genotyping System) to our reference laboratory from October 2021 to September 2023. Our lab performs all the resistance tests from 21 states in México, centers that care for about 2/3 of the cases in the country. In all cases, the test was ordered to detect integrase resistance.

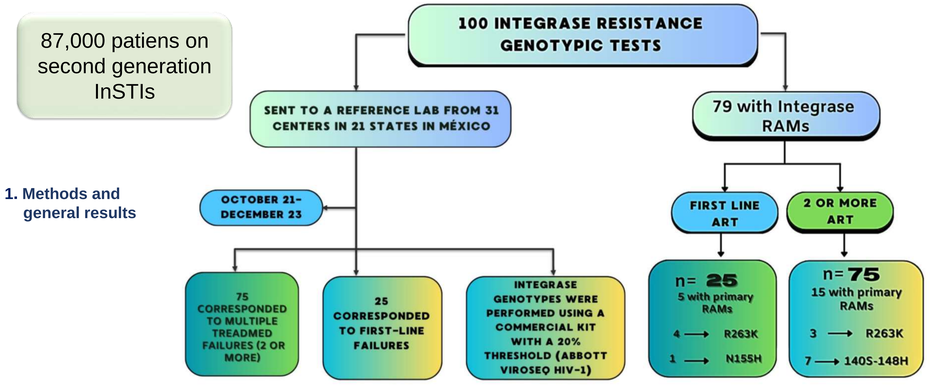

Figure 1. Methods and general results

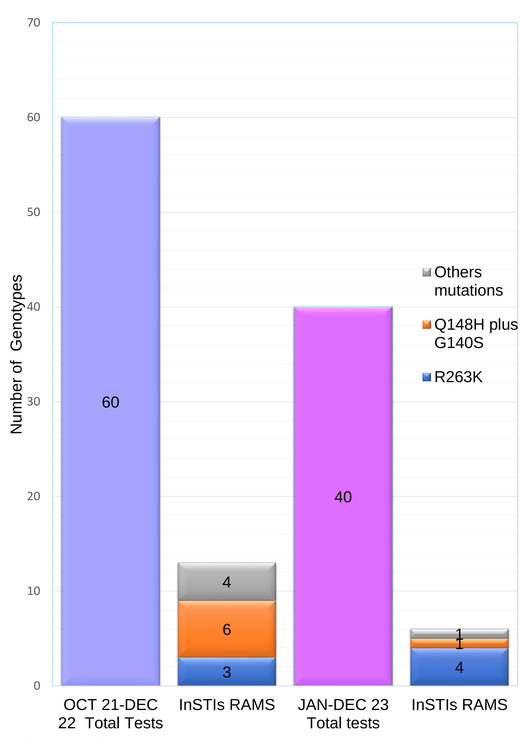

Figure 2. Total integrase resistance genotypic tests performed and p resence of mutations per year

CONCLUSIONS

- Despite the widespread use in México of second generation INSTIs, especially since 2019 when BICTAF has been used as first line treatment and in many switch strategies, the number of failures is limited.
- Only 20/100 of the tests submitted for integrase resistance to our reference laboratory in a 27 months period, had primary mutations in the integrase gene.
- Mutant R263K is present in most INSTI failures when no previous INSTI failure was detected
  - Always in association with M50I in case of BIC failures
  - The combination of R263K plus M50l integrase RAMs is associated with low viral loads at failure
- Failures to multiple ARV treatments (2 or more) showed RAMs patterns related to RAL failure with or without further use of DTG
- **Interestingly NONE of the failures with primary RAMs to integrase resistance, showed M184V in the RT.**

N	Associated RAMs	Current ART	Failure time (Months)	CV at failure	CD4 at failure	Previous treatment (s)
1	E138A	DRV/c+TDF+DTG	10	51683	353	DRV/r+TDF+RAL
2	E138A	FTC+TDF+DTG+DRV/r	22	24846	67	FTC+TDF+EFV
3	E138K	BIC/TAF/FTC	19	264	218	TDF/FTC+EFV
4	L74M+T97A+Y143H	DTG+3TC+ZDV+TDF	17	16541	268	ABC/3TC+TDF+RAL ABC/3TC+ZDV+TDF
5	T97A+E138T+Y143R	BIC/TAF/FTC	2	4776	33	3TC+D4T+LPV/r DDI+3TC+LPV/r 3TC+AZT+NVP TDF/FTC+TPV/r ABC+DDI+ATV/r DRV/r+ETV+DTG+TDF/FTC DRV/r+ETV+DTG DRV/r+ETV+RAL+T20
6	None	DTG+ABC/3TC	16	4576	671	BIC/TAF/FTC DRV/r+RAL
7	None	ETV+DRV/r+DTG	7	266964	460	FTC/TDF+LPV/r

Table 1. Integrase resistance tests with combination of Q148H plus G140S

N	Mutations	Current Scheme	Failure time (Months)	CV at failure	CD4 at failure	Previous treatment (s)
1	**R263K**+V201I+R20K+V21I+T122I	DTG+TDF/FTC	3	298665	22	TDF/FTC+EFV
2	**R263K**+L101I+V201I+V31I+I135V+A49G	DTG+TDF/FTC	21	36320	313	None
3	**R263K**+G118R+E138K+K165N+D256E+I72L+**M50I**+D253E+S230G+I60M	DTG+TDF/FTC	16	1892	178	None
4	**R263K+M50I**	BIC/TAF/ FTC	26	439	45	TDF/FTC+ATV/r
5	**R263K+M50I**+E157Q	BIC/TAF/ FTC	14	2753	58	TDF/FTC+EFV
6	**R263K+M50I**	BIC/TAF/ FTC	13	2153	206	None
7	**R263K+M50I**	BIC/TAF/ FTC	11	4013	137	None

Table 2. Integrase resistance tests with presence of R263K mutation

RESULTS

- One hundred samples were submitted to integrase resistant tests to our referral laboratory in a 27 month period, from an estimated population of 87,000 integrase inhibitors users.
- Eighty resistance genotypes had INSTI-RAMs, but only 20 (20%) had primary resistant mutants, in 13 of them accompanied by secondary mutations. (Figure 1).
- The most common mutants detected were the combination of Q148H plus G140S and the R263K in seven cases each.
- Combination G140S/Q148H was detected in cases failing to DTG(5) and BIC(2), 5 of them with previous RAL failure RAL. (Table 1)
- Mutant R263K increased in frequency from 0.3% (2/666) 2019-21 (reference 1), to 5%(3/60) in 2021-22 and 10% (4/40) in 2023 resistance tests. (Table 2)
  - R263K was detected in 3 cases failing to DTG and 4 to Bictegravir/TAF/emtricitabine, two of them for each integrase used as a first line treatment.
  - Combination of R263K and M50I mutants was present in all cases failing to BIC/TAF/FTC, and in one failing to DTG, all with large failing time (between 11-26 months, and always with low viremias (less than 5,000 copies/ml). (Table 2)
- When RAMs in RT and protease where analyzed, we found mutants in 11 of the 20 cases with primary integrase mutants. None of them had M184V and in 9 cases we found revertants at position 215 of the RT (D/I/S). (Table 3).
- NNRTI mutations were associated to previous EFV use.
- Primary PI RAMs were rare.

ART/ Line	Associated INSTIs	NRTI	NNRTI	PI
DTG+TDF/FTC- 2[a]	R20K+V21I+T122I+V201I+**R263K**	A62Y, T215I	K101E,K103N,V106I	None
BIC/TAF/FTC-1[a]	**M50I+R263K**	T215I	None	None
DRV/c+TDF+DTG-2[a]	E138A+**G140S+Q148H**	None	K103N	None
FTC+TDF+RAL+DRV/r-2[a]	E138A+**G140S+Q148H**	T215I	K103N	None
BIC/TAF/FTC-2[a]	E138K+**G140S+Q148H**	T215I	K103N	None
DTG+3TC+ZDV+TDF-2[a]	L74M+T97A+**G140S+** Y143H+ **Q148H**	I15F, E138K, T215IY, K219E	None	L10I
BIC/TAF/FTC-2[a]	T97A+E138T+**G140S+** Y143R+ **Q148H**	L74V, V75I, T215D	L100I,K103N, V106I	V32I, 154L, R57K, A71V, V82T ,L90M
ETV+DRV/r+RAL-2[a]	**G140S+Q148H**	L74I, E138K	K101E, V179L	L10I, I54L, R57K, A71V
TDF/FTC+RAL-1[a]	N155H	T215I	None	None
TDF/FTC+RAL-2[a]	E138A+G140C+Q148R	M41L, T215IS	K101E, V108I	None
ABC/3TC/DTG-2[a]	L74M+E138K+G140A+S147G +Q148R	L74V, T215I	None	I13V,R41K,R57K,162V, A71V

Table 3. Non–INSTI RAMs In People Failing To 2nd Line Integrase Inhibitors

Reference 1. Resistance to second generation integrase inhibitors after two years of a national rollout strategy in Mexico. Abstract B11,
IAS - International AIDS Society - Conference 2023, Brisbane , Australia.

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