

Integrase inhibitors mutational viral load in HIV infected pregnant women in Argentina

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Background

- Integrase inhibitors (INSTI): raltegravir (RAL) and dolutegravir, constitute preferred options for antiretroviral therapy (ART) in HIV-infected pregnant women (HPW) and RAL is recommended as part of neonatal prophylaxis in high-risk newborns (1, 2).
- In HPW population, Argentina has reported moderate to high levels of transmitted drug resistance to non-integrase drug classes, with high frequency of mutational viral loads (ML) >1000 copies/mL (threshold for highest risk for mother-to-child transmission, formal indication of cesarean section) for non-nucleoside reverse transcriptase inhibitors (3, 4).
- We aim to describe the ML for integrase resistance major and accessory mutations among INSTI-unexposed HPW of an historical cohort (2008-2014).

Material and Methods

- ML was estimated considering baseline viral load value and the obtained frequency of each INSTI resistance mutations by Ultra Deep sequencing (UDS) using a Public Health Agency of Canada genotyping protocol on Miseq sequencer (Illumina) and HyDRA web.
- Stored baseline samples of 56 INSTI-naïve HPW were included (38 ART naïve; 18 exposed to other drug classes) for this analysis.

Results (see also Tables 1 & 2)

- Median (interquartile range, IQR) viral load of the cohort was 15545 (5228-47688) c/mL.
- Prevalence of viral subtypes B and B/F were 21.4 and 78.5%, respectively.
- Major INSTI-mutations were detected at <5% cut-off sensitivity threshold:**
 - Overall prevalence of 8.6% (5/56).
 - Median (range) ML (c/mL) was: 355 (50.2-11705); only 1 case >1000 c/mL (1/56; 1.7%), at expenses of a high baseline maternal viral load (487732 c/mL).
 - ML for Y143C, Y143S, E92G, E138K, T66I resistance-associated mutations were: 63.5, 11705, 49.2, 761.7 and 355 c/mL, respectively (tables 1 and 2).
- Accessory mutations were detected mostly with 20% sensitivity threshold:**
 - Overall prevalence 23.2% (13/56).
 - Median (IQR) ML (c/mL) was: 23929 (4009-63158); all cases >1000 c/mL.
 - The following accessory mutations were described:
 - T97A (2/13), ML: 213449 and 17447, respectively
 - G163K (5/13), median (range) ML: 23929 (3327-62922) and G163R (6/13), median (range) ML: 28614 (1317-154697).
 - A description of ML in each individual sample is shown in tables 1 and 2.

Conclusion

- In a cohort of INSTI-naïve HPW, major integrase resistance associated mutations rarely exceed highest perinatal transmission risk threshold of 1000 copies/mL, as not predominant within viral quasispecies.
- Conversely, accessory mutations exceed this threshold with potential risk of transmission of mutations to the newborn. Clinical impact on maternal ART and neonatal prophylaxis remains to be determined.

References

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Disclosure:

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Table 1. Treatment-Experienced pregnant women in Argentina: INSTI-resistance mutation and HIV Subtype by patient.

Patient #	Overall sample viral load (copies/ml)	Next Generation Sequencing (NGS) findings by thresholds					Subtype
		20%	10%	5%	2%	1%	
		INSTI-resistance mutation (prevalence of viral quasispecies (%), viral load of the mutant quasispecies)					
2018	-	-	-	V151I (5.33%, 107)	V151I (5.33%, 107)	V151I (5.33%, 107)	BF
60507	-	-	-	G163K (5.5%, 3327)	G163K (5.5%, 3327)	G163K (5.5%, 3327)	B
45184	G163R (99.9%, 45138)	G163R (99.9%, 45138)	G163R (99.9%, 45138)	G163R (99.9%, 45138)	G163R (99.9%, 45138)	G163R (99.9%, 45138)	BF
5529	V151I (41.1%, 2272)	V151I (41.1%, 2272)	V151I (41.1%, 2272)	V151I (41.1%, 2272)	V151I (41.1%, 2272)	V151I (41.1%, 2272)	B
55617	G163R (99.9%, 55561)	G163R (99.9%, 55561)	G163R (99.9%, 55561)	G163R (99.9%, 55561)	G163R (99.9%, 55561)	G163R (99.9%, 55561)	BF
70826	G163K (99.9%, 70755)	G163K (99.9%, 70755)	G163K (99.9%, 70755)	G163K (99.9%, 70755)	G163K (99.9%, 70755)	G163K (99.9%, 70755)	BF
12103	G163R (99.9%, 12090)	G163R (99.9%, 12090)	G163R (99.9%, 12090)	G163R (99.9%, 12090)	G163R (99.9%, 12090)	G163R (99.9%, 12090)	BF
487732	S230N (99.5%, 485293)	S230N (99.5%, 485293)	S230N (99.5%, 485293)	Y143S (2.4%, 11705), S230N (99.5%, 485293)	Y143S (2.4%, 11705), S230N (99.5%, 485293)	Y143S (2.4%, 11705), S230N (99.5%, 485293)	B
4706	G163K (99.7%, 4691)	G163K (99.7%, 4691)	G163K (99.7%, 4691)	G163K (99.76%, 4691)	G163K (99.76%, 4691)	G163K (99.76%, 4691)	BF
33147	L74I (99.2%, 32881), S230N (99.3%, 32914)	L74I (99.2%, 32881), S230N (99.3%, 32914)	L74I (99.2%, 32881), S230N (99.3%, 32914)	L74I (99.21%, 32881), S230N (99.31%, 32914)	L74I (99.21%, 32881), S230N (99.31%, 32914)	L74I (99.21%, 32881), S230N (99.31%, 32914)	BF

INSTI: integrase strand transfer inhibitor; PR/TR: protease/reverse transcriptase viral subtype; VL: viral load
Major mutations in bold

Table 2. Treatment-naïve pregnant women in Argentina: INSTI-resistance mutation and HIV Subtype by patient

Patient #	Overall sample viral load (copies/ml)	Next Generation Sequencing (NGS) findings by thresholds					Subtype
		20%	10%	5%	2%	1%	
		INSTI-resistance mutation (prevalence of viral quasispecies (%), viral load of the mutant quasispecies)					
214738	T97A (99.48%, 213621)	T97A (99.48%, 213621)	T97A (99.48%, 213621)	T97A (99.4%, 213449)	T97A (99.4%, 213449)	T97A (99.4%, 213449)	BF
13851	-	-	V151I (14%, 1939)	V151I (14%, 1939)	V151I (14%, 1939)	V151I (14%, 1939)	BF
69941	V151I (100%, 69941)	V151I (100%, 69941)	V151I (100%, 69941)	V151I (100%, 69941)	V151I (100%, 69941)	V151I (100%, 69941)	B
1095	-	-	Y143C (5.8%, 63)	E92G (4.5%, 49), Y143C (5.8%, 63)	E92G (4.5%, 49), Y143C (5.8%, 63)	E92G (4.5%, 49), Y143C (5.8%, 63)	BF
18700	T97A (93.3%, 17447)	T97A (93.3%, 17447)	T97A (93.3%, 17447)	T97A (93.3%, 17447)	T97A (93.3%, 17447)	T97A (93.3%, 17447)	BF
111000	G163R (99.7%, 110667)	G163R (99.7%, 110667)	G163R (99.7%, 110667)	G163R (99.7%, 110667)	G163R (99.7%, 110667)	G163R (99.7%, 110667)	BF
3152	G163R (99.6%, 3139)	G163R (99.6%, 3139)	G163R (99.6%, 3139)	G163R (99.6%, 3139)	G163R (99.6%, 3139)	G163R (99.6%, 3139), Q164P (1.8%, 56)	BF
242473	G163R (63.8%, 154697)	G163R (63.8%, 154697)	G163R (63.8%, 154697)	G163R (63.8%, 154697)	G163R (63.8%, 154697)	G163R (63.8%, 154697), V151I (1.1%, 2667)	BF
3036	G163R (43.4%, 1317)	G163R (43.4%, 1317)	G163R (43.4%, 1317)	G163R (43.4%, 1317)	G163R (43.4%, 1317)	G163R (43.4%, 1317)	BF
26967	V151I (99.5%, 26832)	V151I (99.5%, 26832)	V151I (99.5%, 26832)	V151I (99.5%, 26832)	V151I (99.5%, 26832)	V151I (99.5%, 26832)	BF

INSTI: integrase strand transfer inhibitor; PR/TR: protease/reverse transcriptase viral subtype; VL: viral load
Major mutations in bold