CHANGES IN THE HIV-1 3'-PPT IN PATIENTS FAILING DOLUTEGRAVIR IN BRAZIL

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BACKGROUND

The 3'-polypurine tract (3'-PPT) is a 15 nucleotide long region of the HIV genome. *In vitro* studies showed that mutations in 3'-PPT can cause high-level resistance to dolutegravir and other INSTIs. Whether mutations in the 3'-PPT also lead to INSTI resistance in HIV-1 infected patients is still under debate. Here, we determined the 3'-PPT sequences of HIV-1 infected patients failing DTG-containing cART in Brazil.

Consensus 3'-PPT	A AAA GAA AAG GGG GG
Patient 12	A A**GR** GAA AAG GGG GG
Patient 19	A A**G**A GAA AAG GGG GG
Patient 29	A A**G**A GAA AAG GGG GG
Patient 31	A AAA GAA **C**AG GGG GG
Patient 34	A AAA GAA A**C**G GGG GG
Patient 45	A AAA GAA **M**AG GGG GG

METHODS

- 67 samples from patients failing DTG-containing cART were selected from the biobank of the University of Sao Paulo. Here we report the results of the first 51 patients.
- 3'-PPT sequences of HIV-1 from patients failing DTG containing cART were obtained by Sanger sequencing of total nucleic acid isolated from EDTA whole blood.
- Phylogenetic analysis was used to rule-out cross contamination in the 3'-PPT sequencing procedure.
- For all 3'-PPT sequences that deviated from the consensus 3'-PPT sequence, we calculated the frequency of the observed mutations in 3123 HIV-1 sequences from the Los Alamos database (2018, all subtypes). The binominal distribution was used to calculate the probability of obtaining a particular number of mutations given the frequency obtained from Los Alamos.

RESULTS

- In 6 of the 51 patients, we detected mutations in the 3'-PPT.

patient	RAL pretreatment	Subtype integrase	RAMs in integrase
Patient 12	yes	B	-
Patient 19	no	B	R263K
Patient 29	yes	B	-
Patient 31	no	B	-
Patient 34	yes	B	-
Patient 45	yes	B	-

Mutation	Position in 3' -PPT	Frequency in Los Alamos database	P-value
A → G	3rd	7%	0.23
A → G	4th	0.2%	0.08
A → C	8th	1.1%	0.07
A → C	9th	0.2%	0.08

CONCLUSIONS

- In 3 patients we observed a A → G transition at the 3rd position of the 3'-PPT, which is a polymorphic mutation.
- In the remaining 3 patients we observed mutations in the 3'-PPT at relatively conserved positions.
- The phenotypic effect of the 3'-PPT changes detected here on INSTI susceptibility and HIV-1 replication capacity is still unknown and will be further investigated in our project.

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