The patterns of integrase strand transfer inhibitors drug resistance mutations in HIV-1 CRF06_cpx in Estonia

67

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Background

- The use of integrase strand transfer inhibitors (INSTIs) is increasing across Europe including Estonia.
- The susceptibility to INSTIs varies among HIV-1 subtypes due to dynamic genetic diversity in different HIV-1 variants.
- Major INSTIs drug resistance mutations (DRMs) are at positions T66, E92, E138, G140, Y143, S147, Q148, N155.

Aim

- To describe the distribution of INSTIs DRMs among ART-experienced INSTIs-naive patients and those who have failed INSTIs treatment.

Materials and Methods

Subjects

- 50 INSTIs-naive and 34 INSTIs-failed patients from 2013 to 2017.
- 33 INSTIs-failed patients had experienced raltegravir (RAL) and one patient dolutegravir (DTG) treatment.

Methods

- DRMs detection:
  - HIV-1 integrase region (nucleotides 4141 – 5219, according to HX2B coordinates) sequencing;
  - Stanford University HIV-1 Drug Resistance Database.
- Subtyping: REGA HIV-1 & 2 Automated Subtyping Tool (Version 2.0).

Results

Figure 1. The overall distribution of HIV-1 subtypes in patients sent to DRMs testing. Majority of patients (79%) were infected with HIV-1 CRF06_cpx viruses.

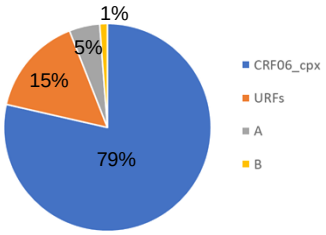
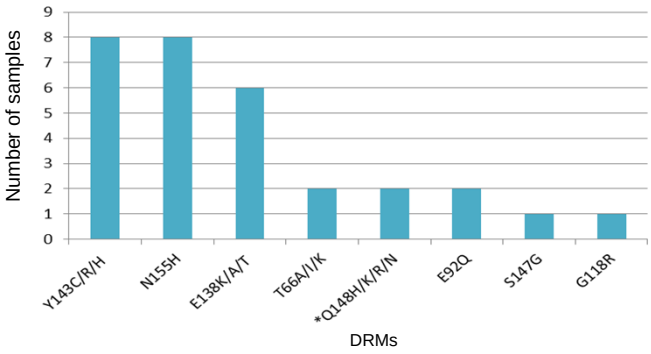


Table 1. Characteristics of patients at the time of DRMs testing

Characteristic	INSTIs-naive N=50	INSTIs-failed N=34
Male, n (%)	34 (68%)	21 (62%)
Median age in years (IQR)	35 (32 – 39)	37 (31 – 39)
Median CD4 count in cells/mm3 (IQR)	160 (82 - 359)[1]	231 (116 – 342)[2]
Median HIV VL in log_{10} copies/mL (IQR)	4.4 (4.1 – 4.9)[3]	4.4 (3.6 – 4.9)[4]
INSTIs DRMs, n (%; 95% CI)	0	20 (59%; 42.2 – 73.6)
Median days between INSTIs initation and resistance (IQR)	-	428 (259 – 570)

[1]CD4 cell count was available for 32 patients; [2]CD4 cell count was available for 23 patients; [3] VL was available for 41 patients; [4] VL was available for 33 patients

- INSTIs DRMs detected in CRF06_cpx viruses from INSTIs-failing patients are indicated in Figure 2.



* DRM which confers intermediate level resistance to the second generation INSTIs

Figure 2. Number of samples carrying INSTIs major drug resistance mutations.

- Most of the detected DRMs alone were associated with high/intermediate resistance to elvitegravir and/or RAL, but low or no resistance to DTG.
- Three viruses carried mutations that conferred intermediate level resistance to DTG (Table 2).

Table 2. Characteristics of patients with DRM profiles which increase the resistance to second generation INSTIs to intermediate level

Patients	Gender	Age	ART history	ART initiation	Integrase mutations
P 1	Male	40	3TC/ZDV + EFV	2011	Y143CHRY, N155HN
			ABC/3TC + LPV/r	2012	
			ABC/3TC + EFV	Dec/2013	
			3TC/ZDV + EFV	Jan/2014	
			3TC/ZDV + RPV	Apr/2014	
			3TC/ZDV + DRV/r	Sep/2014	
			3TC/ZDV + RAL	Jan/2015	
P 2	Female	45	ABC/3TC + EFV	Apr/2011	T66A, S147G, Q148R, E138K
			ABC/3TC + DRV/r	Sep/2011	
			3TC/ZDV + RAL	May/2014	
P 3	Male	58	TDF/FTC + RAL	Jun/2017	E138K, Q148R

Conclusions

- INSTIs DRM-patterns in CRF06_cpx viruses from INSTIs-failing patients are generally same as in other subtypes indicating similar clinical response to the therapy.
- As no INSTIs DRMs were detected in INSTIs-naive patients there is no need for INSTIs DRMs testing prior to INSTIs initiation.
- However, the high prevalence of INSTIs DRMs detected among INSTIs-failed patients suggests an essential need for resistance testing in HIV management with INSTI therapies.

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