Sustained virological response despite K65R along with other resistance mutations in heavily pretreated patients – a Radata subanalysis

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Objective:

The K65R mutation represents a preferred pathway to tenofovir resistance and confers decreased sensitivity to all nucleoside reverse transcriptase inhibitors (NRTIs) except ZDV. Data on outcome of heavily pre-treated patients harbouring K65R is limited.

Methods:

We screened all patients included in the Radata program for the presence of K65R. Radata offers free internet-based support for physicians planning an optimized antiretroviral therapy, based on resistance analysis (RA), drug monitoring and expert advice (EA). Outcome of patients is evaluated prospectively every three months.
Virological response (VR) to new HAART regimen was defined as a viral load < 50 copies/ml at week 48.

Results:

Of 669 patients included in the Radata database, in 20 (3.0 %) the K65R mutations were found. Patients were heavily pre-treated (median no. of prior ART-regimens 4.5, median time on ART 55 months).

Previous NRTIs	100 %		
	3TC 100 %	ZDV 90 %	D4T 74 %
	ABC 68 %	TDF 65 %	DDI 53 %
Previous NNRTIs	100 %		
	NVP 65 %	EFV 60 %	
Previous Pis	85 %		
	IDV 55 %	SQV 45 %	LPV 40 %
	NFV 35 %	APV 20 %	ATV 10 %

Most frequent RT mutations along with K65R were K103N (75 %) and M184V (60 %). All patients had evidence for NNRTI resistance. At least one thymidine analogue mutation (TAM) was found in 35 %.

Table 1: Overview of the patients with K65R who switched HAART

Patient ID	CDC	Time on HAART	No. of previous. regimens	other RT muations than K65R	PI mutations	New HAART	Viral load at switch	Viral load at month 12	Comment
1	A3	57	3	K103N, Y181C	K20I, M36I, V82I	AZT+3TC+ ATV/r	41.000	<50	
2	B3	64	8	M41L, K101E, K103N, L74V, V108I, M184V, Y181C, L210W, T215Y, K219N	L10I, K20I, M36I	LPV/r+SQV	262.000	200.000	Incompliance
3	B3	51	4	K103N, M184V	M36I, L63P, A71T	AZT+3TC+ TDF+LPV/r	1.800	<50	
4	C3	108	8	M41L, A98G, K103N, V75M, F77L, V118I, M184V, L210W, T215Y	L10I, M36I, M46L, I54V, L63P, A71I, V82T, I84V	AZT+3TC+ LPV/r(TPV)	26.200	11.800	
5	C3	24	3	A62V, Y181C, M184V	V82I, I93L	AZT+3TC+ ATV/r	64.000	<50	
6	C3	16	5	A98S, M184V, K103N, V106A	M36I, L63P, I93L	AZT+3TC+ LPV/r	20.065	350	
7	B3	36	4	Q151X, M184V, L100IL, K103N		AZT+3TC+ NFV	5.000	<50	
8	C3	78	4	L100I, M184V, K103N	K20I, M36I, V77I	TDF+3TC+ EFV	186.000	100.000	Incompliance
9	B3	8	1	L100I, M184V, K103N	L63P, V77I, I93L	AZT+ABC+ LPV/r	18.000	<50	
10	B2	54	5	M184V	A71T	AZT+ABC+ 3TC+EFV+ LPV/r	5.390	11.020	
11	C3	33	3	A62V, K103N, F77L, F116Y, Q151M, M184V	L63P, A71T, I93L	LPV/r+IDV	60.000	<50	
12	C3	60	7	K65K	L63P, A71I, V77I, I84V, L90M	DDI+3TC+ ATV/r+T20	1.000.000	<50	
13	C3	59	10	M41L, K101Q, A62V, D67N, V75I, F116Y, V118I, Q151M, T215Y, K219E	L10I, K20I, M36I, I54V, V82A, I84V, L90M	3TC+TDF+ LPV/ r+IDV+T20	60.000	92.000	
14	B3	87	9	A62V, M184V, V108I, Y181C		D4T+3TC+ FPV/r	255	<50	

Results cont.:

Of the 20 patients, 3 did not change their regimen after RA. Two patients were lost to follow up, and one patient died shortly after RA, leaving 14 patients being eligible for analysis. Details are shown in Table 1.

Conclusions/Main findings:

- Prevalence of the K65R mutation was rare (3.0 %) in this large cohort of heavily pre-treated patients.
- Of patients found to harbour K65R, only 65 % had received tenofovir.
- Despite evidence of K65R coincidental with multiple resistance mutations, sustained virological response was possible in 57 % of the cases.
- This was particularly true in the absence of TAMs (73 % versus 0 %, p = 0.05).
- Of patients without additional TAM who switched to an ART containing a thymidine analogue, 75 % had a sustained VR.

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