

Virological response to antiretroviral therapy in the presence of K65R mutation

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Abstract
Introduction: The impact and predictors of K65R mutation on virological response to salvage therapy has not been definitively elucidated.
Methods: We retrospectively identified all K65R mutations in virus samples from 6 Italian clinical centers (4 centers from Genotypic Networking Organization Multicentric Observation). Clinical, viro-immunological and genotypic data were collected and analyzed. Probability of virological response (VR = time to first HIV-RNA <50 cp/ml) and its determinants were calculated using KM and Cox regression.
Results: Overall 145 patients were included. The mean number of NRTI used was 4 (range 2-7). At the time of genotyping (GRT), the most frequent administered NRTIs were: TDF (56.5%), 3TC (56.5%), ddI (55.7%), and d4T (22.9%). Median HIV-RNA and CD4 count were 4.17 log₁₀ copies/mL (IQR: 3.62-4.73) and 312 cells/mm³ (IQR: 148-471). M184V was detected in 44.8%, and S66GN/R/K in 27.6%; at least one mutation from Q151M-complex, TAMs1, and TAMs2 pathways was found in 31.7%, 15.2%, and 22.8%, respectively.
 After GRT, the most frequent NRTI was 3TC (59.7%), AZT (29.0%), d4T (27.4%), and ddI (23.4%). Over a total of 197 PVPV, the 12-month probability of VR was 60% (SE 5%); this probability was strongly reduced by the Q151M pathway (52% vs 65%; P=0.02 at log-rank test). By multivariate Cox model the strongest predictors of VR were adding a thymidine analogue (TA) in the salvage regimen (HR 2.55; 95%CI 1.25-5.19; P=0.01); in a separate model the relative risk of VR by TA was higher for d4T (2.66; 1.05-6.72; P=0.04) than for AZT (1.64; 0.63-4.24; P=0.31). Moreover, M184V (1.97; 1.00-3.86; P=0.05) was associated with a better outcome, even there was no evidence of interaction with 3TC use (P=0.56 at interaction-test). Furthermore, the presence of LPV/r as new drug was marginally associated with better outcome (1.73; 0.95-3.18; P=0.07). Excluding subjects with Q151M, use of thymidine analogue as a new drug had a slight effect (2.07; 0.96-4.46; P=0.06) on VR, that was strongly reduced by viremia at baseline (0.59; 0.37-0.94; P=0.03). Even in this model, the effect of M184V remained favorable (2.26; 1.00-5.08; P=0.05).
Conclusions: Development of K65R mutation does not preclude the effectiveness of rescue therapy. Inclusion of a thymidine analogue in the salvage regimen (DAT rather than AZT) as well as low-level viremia at change predict better response. Concomitant presence of M184V may have a favorable effect on virological outcome.

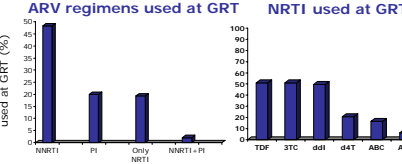
Background
 • Although the K65R mutation remains relatively uncommon, reports from some large-database of resistant HIV-strains have shown a significant increasing trend in its prevalence concomitantly with the widely use of TDF in clinical practice.
 • The importance of K65R mutation lies in its possible role in multi-NRTI resistance, which could compromise the chances of rescue in HIV patients treated with nucleoside analogues
 • At present, there is little information to guide clinical decision-making with respect to patients with virologic failure associated with the emergence of the K65R mutation.

Objectives
 • To define the impact of K65R mutation on virological response to salvage therapy
 • To assess clinical and virological determinants of treatment success

Methods
 • Retrospective analysis on all K65R mutations identified in virus samples for 6 Italian clinical centers (4 centers from Genotypic Networking Organization Multicentric Observation)
 • All therapeutic, clinical, viro-immunological and genotypic data were collected in a database and analysed
 • Probability of virological response (VR = time to first HIV-RNA <50 cp/ml), and its determinants were calculated using Kaplan-Meier and Cox model

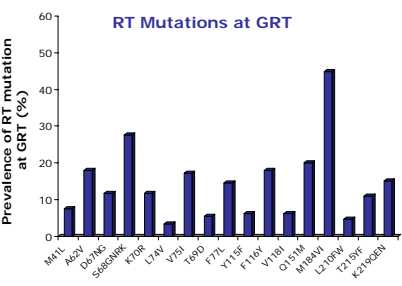
Results

General characteristics	
Variables	Patients (n=145)
Gender M, n (%)	114 (78.6)
Age (years), mean (range)	41 (25-72)
Mode of HIV acquisition, n (%)	
- Heterosexual intercourse	61 (42.1)
- IDU	40 (27.6)
- MSM	26 (17.9)
HIV-RNA levels, log ₁₀ cp/ml median (IQR)	4.17 (3.62-4.73)
CD4 cell/mm ³ , median (IQR)	312 (148-471)
Therapeutic characteristics	
Time on antiretroviral therapy, median (IQR)	37 (19-62) mo.
N° of therapeutic failures, median (IQR)	2 (1-3)
N° of ARVs previously used, mean (range)	
- NRTI	4 (1-7)
- NNRTI	1 (0-2)
- PI	2 (0-6)
Type of previous NRTI exposure, n (%)	
3TC previous exposure	117 (80.7)
ddI previous exposure	106 (73.1)
d4T previous exposure	98 (67.6)
AZT previous exposure	92 (63.4)
TDF previous exposure	68 (46.9)
ABC previous exposure	40 (27.6)
ddC previous exposure	29 (20.0)



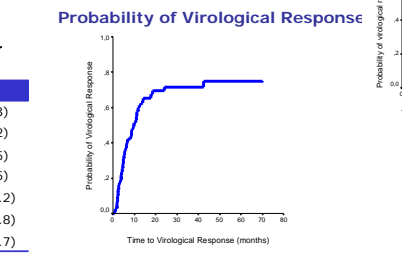
Genotypic mutation pattern at baseline

Number of PI mutations, median (IQR)	2 (1-3)
Number of NNRTI mutations, median (IQR)	1 (0-2)
Number of NRTI mutations, median (IQR)	3 (2-5)
Number of TAMs, mean (range)	1 (0-5)
- One from Type 1 TAMs (M41L, L210W, T215Y), n (%)	22 (15.2)
- One from Type 2 TAMs (D67N, K70R, K219Q), n (%)	33 (22.8)
One from Q151M-complex, n (%)	46 (31.7)



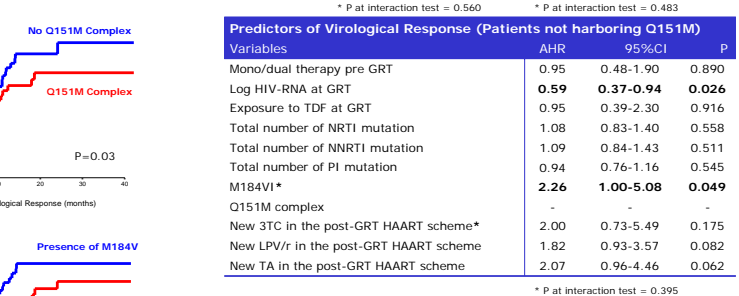
Characteristics of post-GRT therapy

PI-containing regimen	
- LPV/r	38.6%
- NFV	10.3%
- ATZ	8.3%
- SOV	5.5%
- IDV	5.5%
- APV or fosAPV	4.2%
NNRTI-containing regimen	
- EFV	8.3%
- NVP	6.2%
NRTI used in the post-GRT therapy	
- 3TC	51.0%
- AZT	24.8%
- d4T	23.4%
- ddI	20.0%
- TDF	18.6%
- ABC	17.9%



Predictors of Virological Response (All pts.)

Variables	MODEL 1			MODEL 2		
	AHR	95%CI	P	AHR	95%CI	P
Mono/dual therapy pre GRT	1.19	0.66-2.14	0.568	1.17	0.65-2.11	0.61
Log HIV-RNA at GRT	0.73	0.50-1.07	0.106	0.73	0.50-1.06	0.10
Exposure to TDF at GRT	1.56	0.70-3.45	0.276	1.40	0.61-3.19	0.42
Total number of NRTI mutation	0.97	0.74-1.26	0.814	0.94	0.71-1.24	0.65
Total number of NNRTI mutation	1.01	0.82-1.26	0.868	1.03	0.83-1.27	0.81
Total number of PI mutation	1.02	0.87-1.19	0.800	1.01	0.87-1.19	0.87
M184V*	1.97	1.00-3.86	0.049	1.99	1.01-3.91	0.05
Q151M complex	0.94	0.66-1.34	0.743	0.96	0.67-1.38	0.83
New 3TC in the post-GRT HAART scheme*	1.82	0.67-4.93	0.238	1.86	0.68-5.04	0.22
New LPV/r in the post-GRT HAART scheme	1.73	0.95-3.17	0.075	1.81	0.98-3.34	0.06
New TA in the post-GRT HAART scheme	2.55	1.25-5.19	0.010	-	-	-
New AZT in the post-GRT HAART scheme	-	-	-	2.05	0.87-4.82	0.10
New d4T in the post-GRT HAART scheme	-	-	-	3.32	1.39-7.96	0.01



Conclusions

- Development of K65R mutation does not preclude the effectiveness of rescue therapy
- Inclusion of a thymidine analogue in the salvage therapy as well as low-level viremia at change predict better response
- Concomitant presence of M184V may have a favorable effect on virological outcome



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