THE EFFECT OF NUMBER OF MUTATIONS AND DRUG-CLASS SPARING ON VIROLOGIC RESPONSE TO SALVAGE GENOTYPE-GUIDED ANTIRETROVIRAL THERAPY

National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy

B.C. CIANCIO, M.P. TROTTA, P. LORENZINI, F. FORBICI, U. VISCO-COMANDINI, P. MARCONI, C. GORI, S. BONFIGLI, M.C. BELLOCCHI, M. ZACCARELLI, R. D'ARRIGO, V. TOZZI, E. BOUMIS, P.NARCISO, C.F. PERNO, A. ANTINORI

Background

- **Among GRT-related factors influencing response to antiretrovirals, a significant association between the number of mutations conferring drug resistance at baseline GRT and subsequent virologic response was estabilished in several retrospective studies.**
- **The effect of the number of resistance mutations on the virologic outcome has not been investigated in detail in prospective clinical trials.**
- **Clear-cut correlations between number of mutations and efficacy of GRT-guided therapy are still missing in large longitudinal studies.**

Objectives

- **To assess wether, and at which amount, the number of drug-associated mutations and history of previous exposure to antiretrovirals affect virologic response to GRT-guided therapy in a large unselected cohort of HIV positive subjects with virologic failure to HAART.**

Methods

Patients: all consecutive patients who failed different HAART regimens and performed a genotypic resistance test at one HIV/AIDS reference center in Rome

Period: June 1999 – March 2002

Design: prospective observational study

Genotypic resistance test: genotypic sequencies fo HIV was analyzed by Viroseq-2 and an expert advice was offered to physicians.

Data collection: demographic and epidemiological characteristics, clinical events, viro-immunological parameters and therapeutic history were collected for each patient

Statistical analysis

- **Outcome: virologic success (<80 cp/ml HIV-RNA level during the follow-up time).**
- **Main exposures: total number of mutations conferring resistance to PI, NRTI and NNRTI (mutations considered in the anlysis were all those recently reported by the Drug Resistance Mutations Group of the International AIDS Society-USA).**
- **Confouders: numbers of previous failure to HAART, CD4 and HIV-RNA at GRT, history of previous exposure to PI and NNRTI.**

- **The effect of each addictional mutation on the likelihood of reaching undetectable HIV-RNA plasma level was measured using univariate Cox analysis.**
- **The total number of PI, NRTI and NNRTI were divided in categories for which crude and adjusted rates of the outcome were calculated by Cox analysis in three different models.**
- **The probability of reaching virologic success according to number of mutations and drug exposure was estimated by Kaplan Meyer curves.**

Patients characteristics at GRT (n=470)

Demographic characteristics:

- Gender, M:		69%
- Median age, *years (SD)*:		39 (7.6)
- Risk factor for HIV:	- IVDU=	145 (30.9%)
	- Heterosexual=	146 (31.1%)
	- MSM=	76 (16.2%)
	- Other/Unknown =	43 (9.2%)

HIV-related variables:

- Previous AIDS:	176 (37%)
- median CD4 cell at GRT (IQR)	300/ml (159-464)
- median HIV-RNA at GRT (IQR)	4.46 $\log_{10}$cps/ml (3.92-5.03)

Patients characteristics: treatment related variables (n=470)

Time on HAART, *months*	
- overall, *mean (± SD)*	27.6 (±14.7)
Number of HAART failures, *mean (± SD)*	3.1 (±1.99)
- first failure, *n (%)*	112 (25%)
Exposure to ARV, *n (%)*	
NNRTIs	238 (51)
PIs	391 (83)
all classes	185 (39)
Total mutations at GRT, *median (range)*	
NRTI-related mutations	3 (0.0-8.0)
PI-related mutations	3 (0.0-10.0)
NNRTI-related mutations	0 (0.0-3.0)

Probability of virologic success according to number of mutations

A proportion of 42% (188/470) subjects reached undetectable viremia

Exposure	Probability of HIV-RNA<80 cp/ml	P
Each added NRTI-related mutation	0.92 (0.86-0.98)	0.01
Each added PI-related mutation	0.92 (0.87-0.97)	0.002
Each added NNRTI-related mutation	0.63 (0.46-0.85)	0.003

Likelihood of virologic success (univariate)

Variables	Categories	RR (95%CI)	P
Number of NRTI resistance mutations	0-1	Ref	
	2-3	1.29 (0.90-1.86)	0.450
	4-5	0.85 (0.59-1.23)	0.975
	>6	0.51 (0.29-0.90)	0.02
Number of PI resistance mutations	0-1	Ref	
	2-3	0.79 (0.53-1.19)	0.263
	4-6	0.94 (0.65-1.36)	0.749
	≥ 7	0.52 (0.33-0.82)	0.005
Number of NNRTI resistance mutations	0	Ref	
	1	0.76 (0.53-1.09)	0.133
	≥ 2	0.49 (0.31-0.78)	0.003
Previous exposure PI	no	Ref	
	Yes	0.64 (0.44-0.93)	0.019
Previous exposure NNRTI	No	Ref	
	Yes	0.67 (0.50-0.90)	0.007
Previous exposure to all classes	No	Ref	
	Yes	0.49 (0.36-0.68)	<0.001

Likelihood of virologic success. Multivariate with number of NRTI mutations

Exposure's Categories	RR (95%CI)	P
0-1	Ref	
2-3	1.36 (0.91-2.05)	0.129
4-5	0.94 (0.63-1.41)	0.771
>6	0.71 (0.39-1.29)	0.258

Likelihood of virologic success. Multivariate with number of PI mutations

Variables	Exposure's Categories		RR (95%CI)	P
Total n. of PI mutations	0-1		Ref	
	2-3	NNRTI naive	0.64 (0.36-1.14)	0.127
		NNRTI exposed	0.89 (0.52-1.55)	0.686
	4-6	NNRTI naive	1.20 (0.66-2.16)	0.550
		NNRTI exposed	0.86 (0.43-1.73)	0.673
	≥ 7	NNRTI naive	1.12 (0.59-2.12)	0.734
		NNRTI exposed	0.25 (0.11-0.60)	0.002
Previous NNRTI exposure	no		Ref	
	Yes	0-1 PI mutations	0.90 (0.51-1.58)	0.703
		2-3 PI mutations	1.29 (0.76-2.19)	0.352
		4-6 PI mutations	0.68 (0.35-1.34)	0.272
		≥ 7 PI mutations	0.20 (0.08-0.48)	<0.001

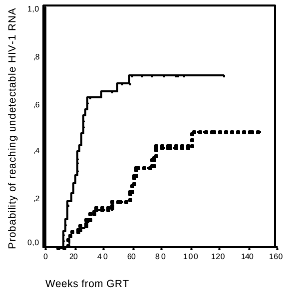
Interaction term *number of PI mutations*previous NNRTI exposure* was significant (P=0.002)

Likelihood of virologic success. Multivariate with number of NNRTI mutations

Variables	Exposure's Categories		RR (95%CI)	P
Total n. of NNRTI mutations	0		Ref	
	1	PI naive	1.46 (0.62-3.43)	0.389
		PI exposed	0.59 (0.32-1.08)	0.087
	≥ 2	PI naive	0.88 (0.31-2.47)	0.811
		PI exposed	0.44 (0.23-0.87)	0.017
Previous PI exposure	no		Ref	
	Yes	0 NNRTI mutations	0.91 (0.47-1.75)	0.770
		1 NNRTI mutations	0.43 (0.16-1.19)	0.106
		≥ 2 NNRTI mutations	0.54 (0.16-1.76)	0.305

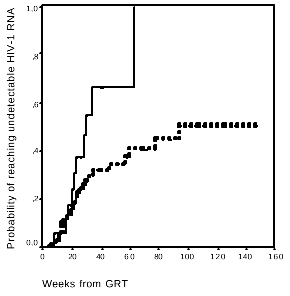
Interaction term *number of NNRTI mutations*previous PI exposure* was significant (P=0.050)

K-M cumulative probability of virologic success



K-M cumulative probability of reaching undetectable viral load after GRT in patients with ≥7 mutations for PI by previous exposure to NNRTI (continous line for NNRTI-naive and dashed line for NNRTI-experienced)

K-M cumulative probability of virologic success



K-M cumulative probability of reaching undetectable viral load after GRT in patients with ≥2 mutations for NNRTI by previous exposure to PI (continous line for PI-naive and dashed line for PI-experienced)

Conclusions

- **High rates of virologic response are achievable using a GRT-guided antiretroviral therapy even in subject with a high number of mutations to PI and NRTI.**
- **Even few NNRTI resistance associated mutations are sufficient to significantly reduce the chances of success of GRT-guided therapy.**
- **Our study identify three thresholds for each drug class (>7 for PI, >6 for NRTI and >2 for NNRTI), above which the number of mutations had a significant effect on virologic outcome.**
- **The probability of reaching virologic success was not affected by ana high number of mutations both for PI and NNRTI if patients had a new class to which they had never been exposed or if the GRT showed absence of mutations for NNRTI or PI.**
- **Knowledge of the GRT profile as well as the expert advice could allowed the identification of residual antiretrovirals for which the virus was still, even partially, sensible enhancing the chances of virologic success even in presence of a high number of drug resistance mutations.**