Pre-Existing Low-Levels of the K103N HIV-1 RT Mutation Above a Threshold is Associated with Virological Failure in Treatment-Naïve Patients Undergoing EFV-Containing Antiretroviral Treatment

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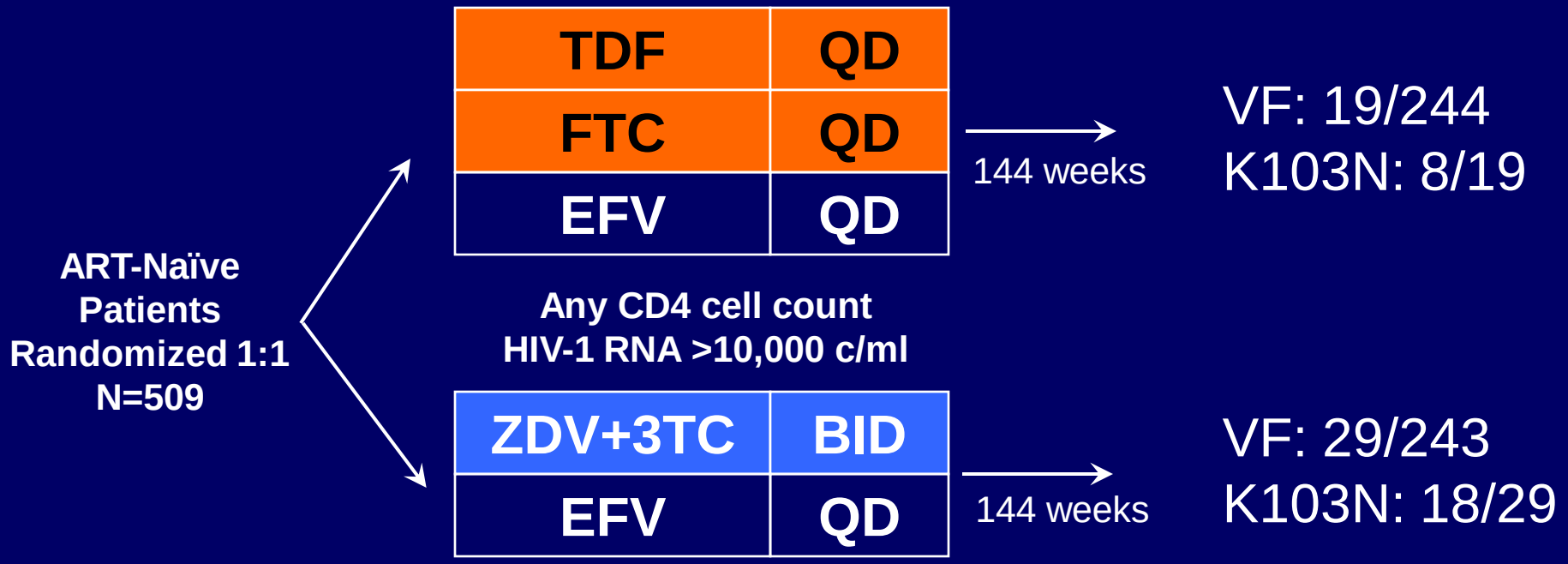


- 22/509 patients were excluded from analysis due to the presence of NNRTI resistance mutations at BL by population sequencing

- Virologic Failure (VF) defined as confirmed HIV-1 RNA of >400 copies/ml at week 144 or early discontinuation

Objectives

- **To test all baseline samples from study GS-01-934 for the presence of minor sub-populations of the K103N mutation**

- **To determine if there is a correlation between pre-existing low-levels of K103N at baseline and virologic failure**

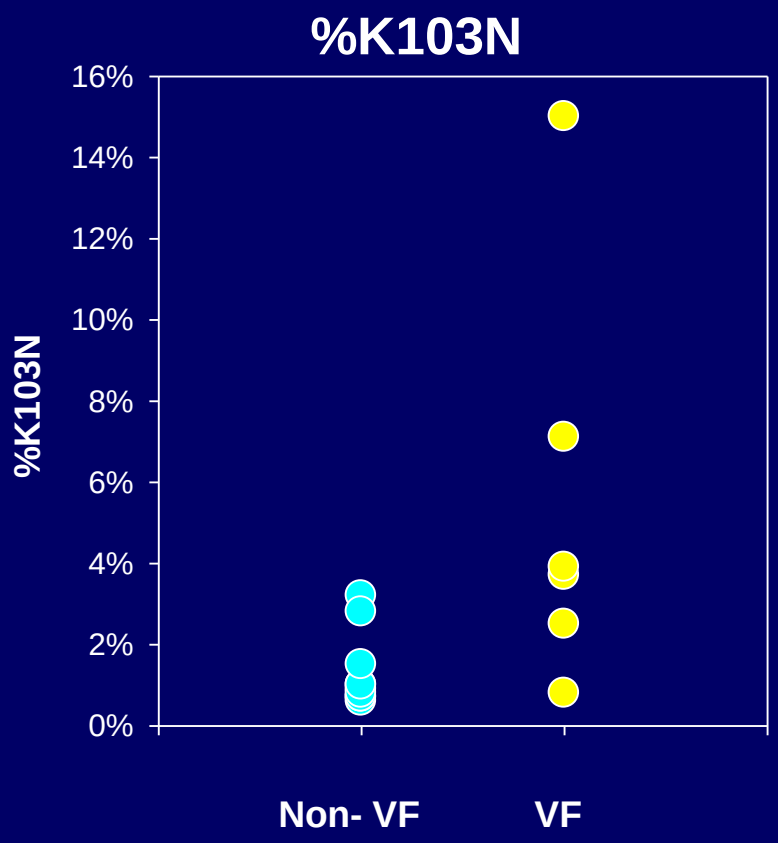
Methods: All available baseline plasma samples from patients were RT-PCR amplified and tested for K103N by AS-PCR with a cut-off at 0.5%

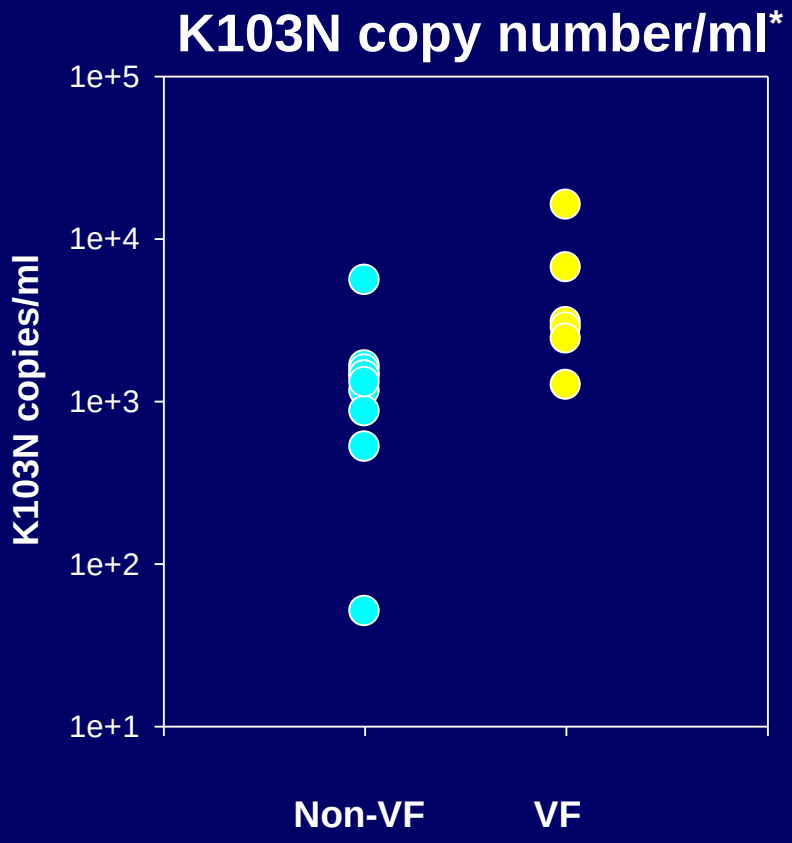
Low Levels of K103N Correlated with VF

	TDF+FTC+EFV	ZDV+3TC+EFV	Total
	n=244	n=243	n=487
AS-PCR results	239	237	476
K103N positive	5	11	16
VF	1 (20%)	5 (45%)*	6 (38%)**
non-VF	4	6	10
K103N negative	234	226	460
VF	18 (8%)	24 (11%)*	42 (9%)**
non-VF	216	202	418

*Fisher's Exact test, p = 0.005 (5/11 vs. 24/226)
** Fisher's Exact test, p = 0.003 (6/16 vs. 42/460)

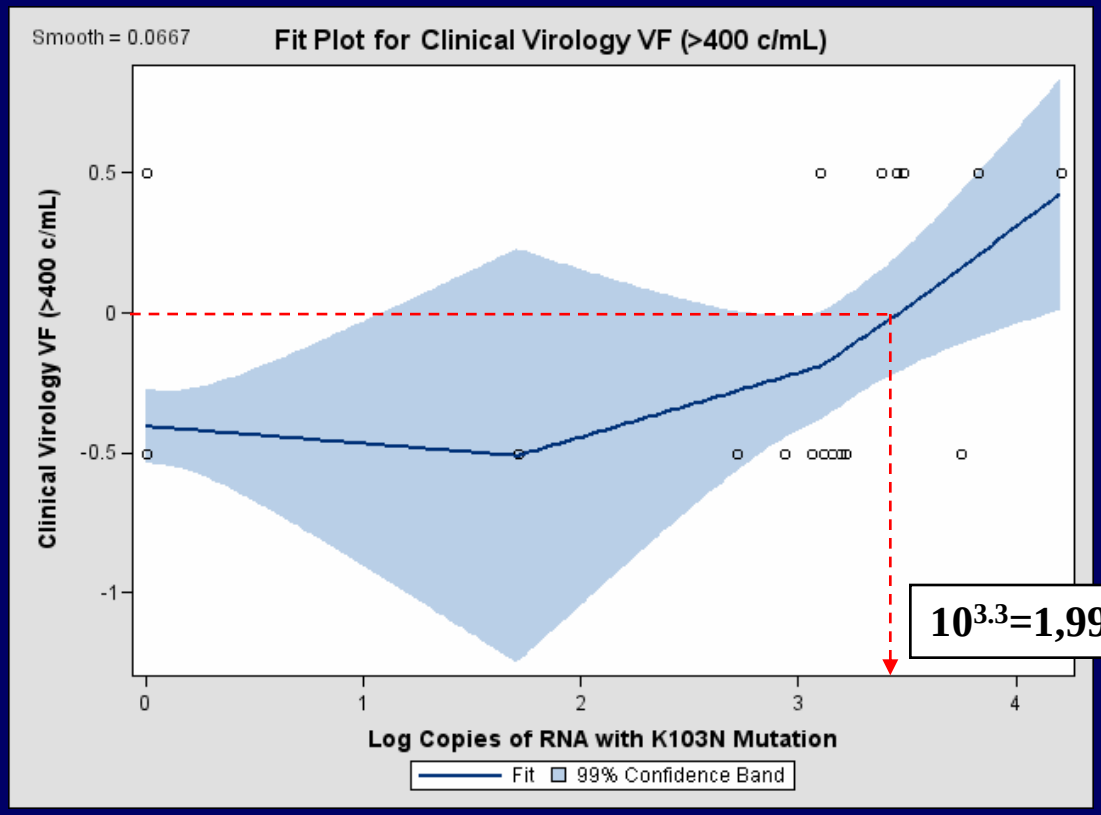
Virologic Failure Appears to Partition by K103N Copy Number at Baseline





* K103N copy number/ml = (%K103N) x (Baseline Viral Load)

A Threshold Quantity of > 2000 Copies of K103N at Baseline May Predict VF



VF

non-VF

$10^{3.3}$=1,995 c/ml

K103N at BL > 2000 copies/ml and Risk of VF

• Multivariate logistic regression to predict risk of VF with predictors treated as categorical variables

Baseline Parameter	Odds Ratio (95% CI)	P-Value Chi-Square test
K103N >= 2,000 copies/mL	47.4 (5.2, 429.2)	0.0006
K103N detectable and < 2,000 copies/mL	1.19 (0.15, 9.71)	0.8703
BL HIV RNA >100,000	0.98 (0.51, 1.88)	0.9471
BL CD4 >=200	0.60 (0.31, 1,16)	0.1282
Treatment arm	0.75 (0.40, 1.41)	0.3695

• K103N >2% was also predictive of VF with Odds Ratio = 25.5 and P = 0.0002

• For ZDV+3TC+EFV arm alone, K103N >2000 copies/ml was also predictive of VF with Odds Ratio = 45.4 and P = 0.0007

Conclusions

- In this study, the presence of low-level K103N at baseline as detected by AS-PCR was associated with increased risk of VF
  - Similar results were obtained within the ZDV+3TC+EFV arm alone
  - There were insufficient numbers of VF patients in the TDF+FTC+EFV arm to establish the risk associated with low-level K103N
- A threshold quantity of K103N at baseline was predictive of VF for patients on an EFV-containing triple drug combination:
  - 6/16 K103N positive patients had >2000 K103N copies/ml with 5/6 failing therapy
  - 10/16 K103N positive patients had <2000 K103N copies/ml with 9/10 patients showing treatment response through week 144
- Overall in the study, 6/476 (1.3%) subjects were found to have a sub-population of K103N at baseline of > 2000 copies/ml and increased risk of VF
- Further studies are needed to establish the relevance of threshold quantities of drug resistant mutants for other drug therapies

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