

Baseline phenotypic susceptibility and virologic failure over 144 weeks among nucleoside RT inhibitor experienced subjects in ACTG 364.

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Background

Phenotypic testing for drug resistance may identify patients at risk for virologic failure (VF). Phenotypic susceptibility scores (PSS) incorporating treatment regimen were assessed over 144 weeks for virologic outcome in 131 highly nucleoside-experienced subjects from ACTG 364 assigned 2 nucleosides + NFV (46), EFV (45) or both (40) (see Table 1).

Methods

Phenotypic susceptibility was analyzed from plasma samples using a recombinant assay (ViroLogic)(Figure 1). Dichotomous and continuous PSS were assigned based on drug treatment and susceptibility (fold-change) of the subject's baseline (BL) isolate (below). Time to confirmed VF (two consecutive HIV RNA levels $\geq 2,000$ c/mL at week ≥ 16) on initial study treatment was assessed by Cox proportional hazards regression, adjusting for BL \log_{10} HIV RNA, and Kaplan-Meier curves. Phenotypic sensitivity was defined as ≤ 1.5 -fold increase in IC_{50} relative to control for ddI and d4T and ≤ 2.5 -fold for other ACTG 364 drugs (3TC, EFV, NFV). Hypersusceptibility to EFV (HS), defined as a fold-change of ≤ 0.4 , was considered as a dichotomous, independent variable.

Results

Higher PSS was significantly associated with lower risk for VF with both a continuous ($p=0.001$) and dichotomous ($p=0.004$) score, adjusting for BL HIV RNA (Table 2). Number of new 364 drugs ($p<0.001$), but not BL CD4, was also significantly associated with outcome. When analyses were restricted to the 91 subjects on triple-therapy arms (NFV or EFV + 2 nRTIs), PSS demonstrated a trend towards decreased risk of VF ($p=0.096$). A model to examine EFV HS in the two EFV-containing arms showed 3 significant covariates associated with reduced risk of VF: lower BL HIV RNA ($p=0.032$), higher continuous PSS ($p=0.003$), and EFV HS ($p=0.042$) (Table 3).

Calculations of Continuous Phenotypic Susceptibility Score

A continuous PSS was calculated after assigning a value of 1 to each drug in the treatment regimen with a measured phenotypic fold-change ≤ 2.5 (≤ 1.5 for didanosine and stavudine), 0 for drugs with a fold-change >10 , and a value between 0 and 1, calculated as $1 - (\text{fold-change} - 2.5)/(10-2.5)$, for drugs with fold-change between 2.5 (1.5 for didanosine and stavudine) and 10.

Conclusions

Lower BL viral load, a higher PSS score (receipt of more active drugs), and EFV HS were independently associated with a lower risk for VF. The PSS based on lower cut-off values for ddI and d4T was significantly associated with virologic outcome among highly nucleoside-experienced subjects over 144 weeks. Additional clinical studies are needed to validate biological cut-offs for d4T and ddI and to assess whether EFV HS augments viral suppression during nRTI+EFV treatment in nRTI experienced patients.

Figures and Tables

Figure 1: Baseline Phenotypic Susceptibility

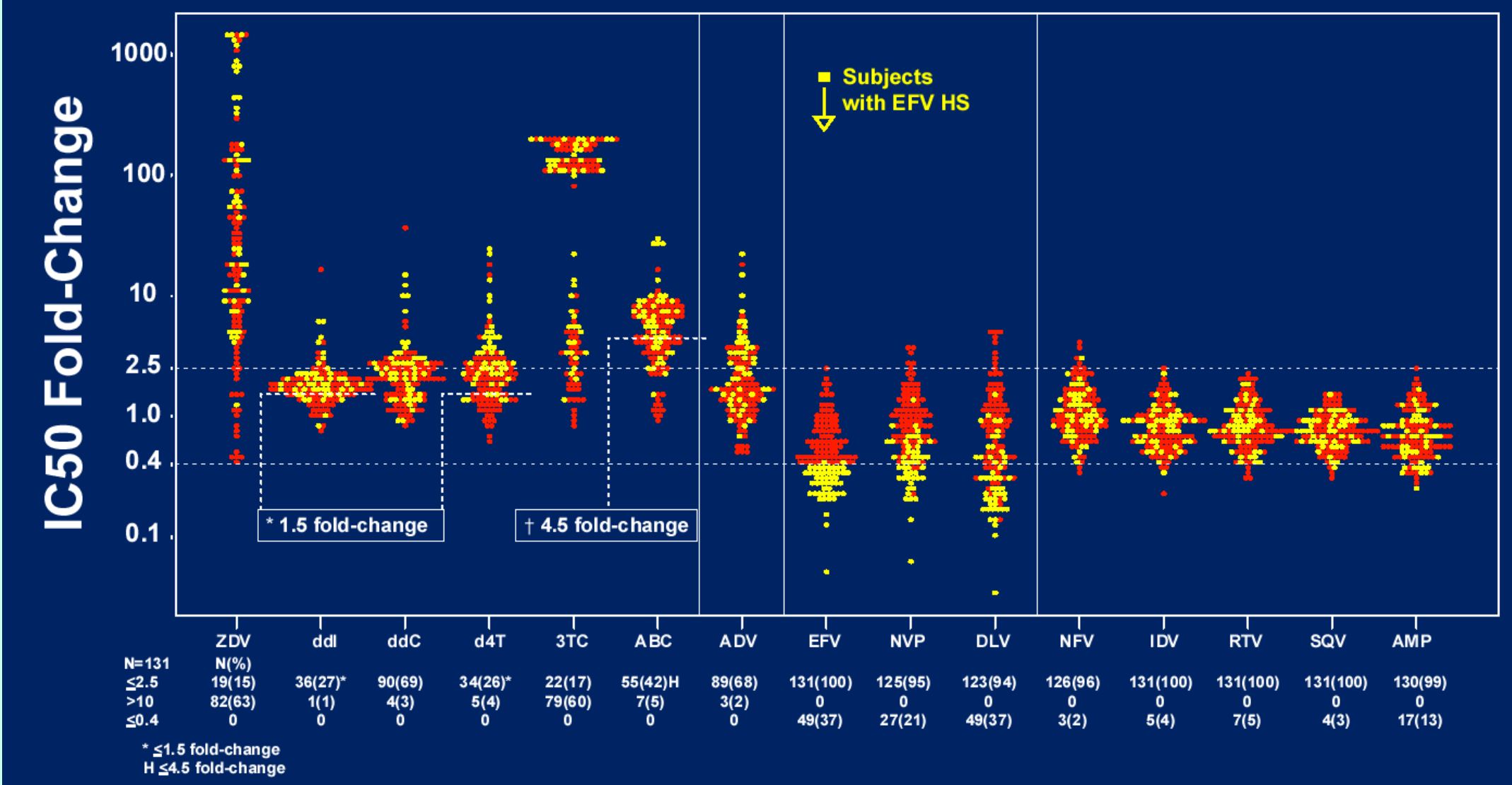


Figure 2: Time to Virologic Failure (Confirmed HIV RNA ≥ 2000)

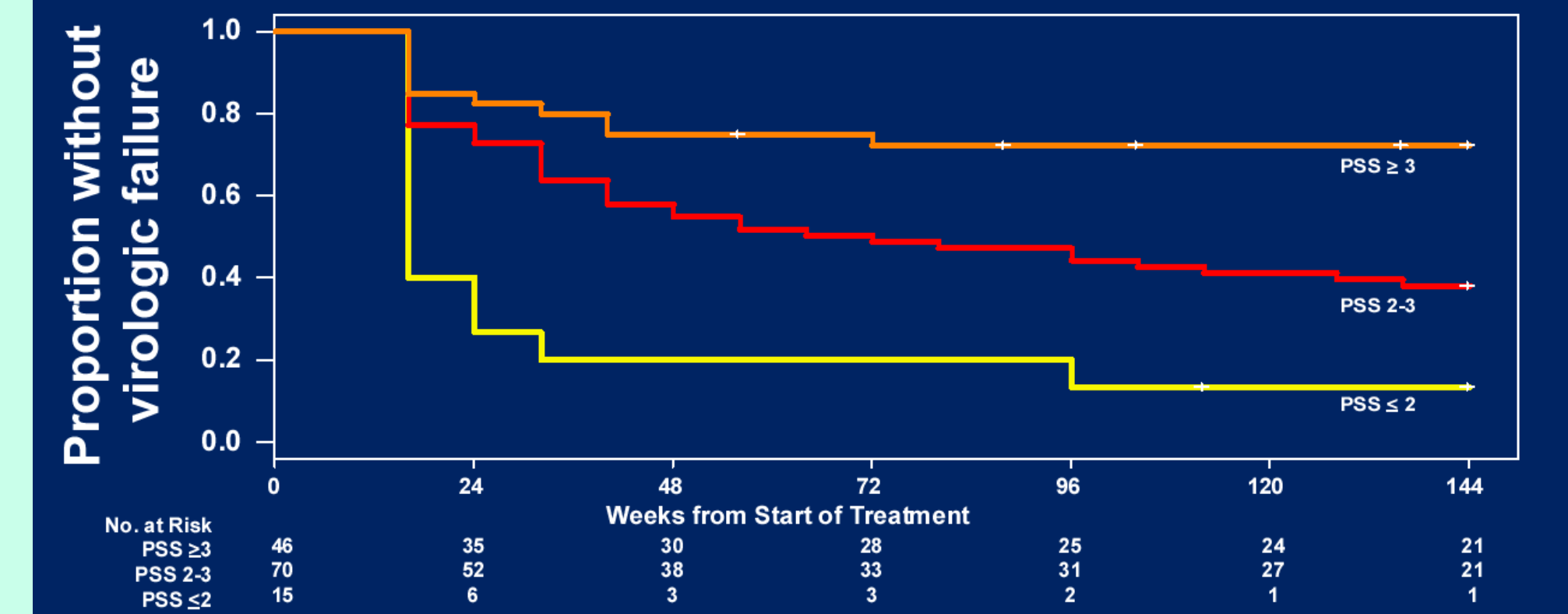


Table 2: Cox Proportional Hazards Models for Predicting Virologic Failure

	Model	Hazard Ratio (95% CI)	p-value
Univariate	1 \log_{10} higher baseline RNA	1.61 (1.10 – 2.36)	0.014
	Number of 364 new drugs (1 additional new drug)	0.36 (0.24 – 0.53)	<0.001
	Phenotypic Sens. Score – Dichotomous (1 unit higher)	0.62 (0.44 – 0.88)	0.007
	Phenotypic Sens. Score – Continuous (1 unit higher)	0.53 (0.37 – 0.75)	<0.001
Multivariate	1 \log_{10} higher baseline RNA	1.82 (1.23 – 2.68)	0.003
	Number of 364 new drugs	0.33 (0.22 – 0.50)	<0.001
	1 \log_{10} higher baseline RNA	1.68 (1.15 – 2.46)	0.008
	Phenotypic Sens. Score – Dichotomous	0.60 (0.42 – 0.85)	0.004
Multivariate	1 \log_{10} higher baseline RNA	1.59 (1.09 – 2.34)	0.017
	Phenotypic Sens. Score – Continuous	0.54 (0.38 – 0.76)	<0.001

Table 1: Baseline Characteristics by Whether or Not in Baseline Phenotype Analysis

		Included in baseline phenotype analysis	
		Yes (N=131)	No (N=64)
Male:			
ACTG 364 Treatment:	NFV+2 RTIs	46 (35%)	20 (31%)
	EFV+2 RTIs	45 (34%)	20 (31%)
	NFV+EFV+2 RTIs	40 (31%)	24 (38%)
ACTG 364 Assigned Dual Nucleoside Therapy:	d4T+ 3TC	58 (44%)	25 (39%)
	ddI+ 3TC	8 (6%)	2 (3%)
	ddI+ d4T	65 (50%)	37 (58%)
HIV RNA (\log_{10} c/mL)*	Median (25 th -75 th)	4.17 (3.67,4.61)	3.09 (2.80,3.32)
CD4 Cell Count (mm^3)**	Median (25 th -75 th)	336 (240,469)	422 (282,534)
Prior NRTI exposure > 52 weeks:	ZDV	131 (100%)	63 (98%)
	ddI	74 (56%)	44 (69%)
	ddC	40 (31%)	9 (14%)
	d4T	8 (6%)	2 (3%)
	3TC	81 (62%)	48 (75%)
Number of 364 New Drugs:	2	33 (25%)	21 (33%)
	3	69 (53%)	31 (48%)
	4	29 (22%)	12 (19%)

* $p<0.001$ comparing those subjects included versus those not included in the phenotypic analysis.

** $p=0.026$.

Table 3: In EFV-Containing arms (N=85) Cox Proportional Hazards Models for Predicting Virologic Failure.*

		Hazard Ratio (95% CI)	p-value
Multivariate	1 \log_{10} higher baseline RNA	1.79 (1.05 – 3.04)	0.032
	Phenotypic Sens. Score – Continuous	0.43 (0.24 – 0.74)	0.003
	EFV Hypersusceptibility	0.43 (0.19 – 0.97)	0.042

* EFV HS not associated with VF in the same model applied to subjects in the NFV arm (N=46, $p=0.93$)