Antiretroviral resistance in ACTG 388 participants with Virologic failure

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for the ACTG 388 Resistance Study Team

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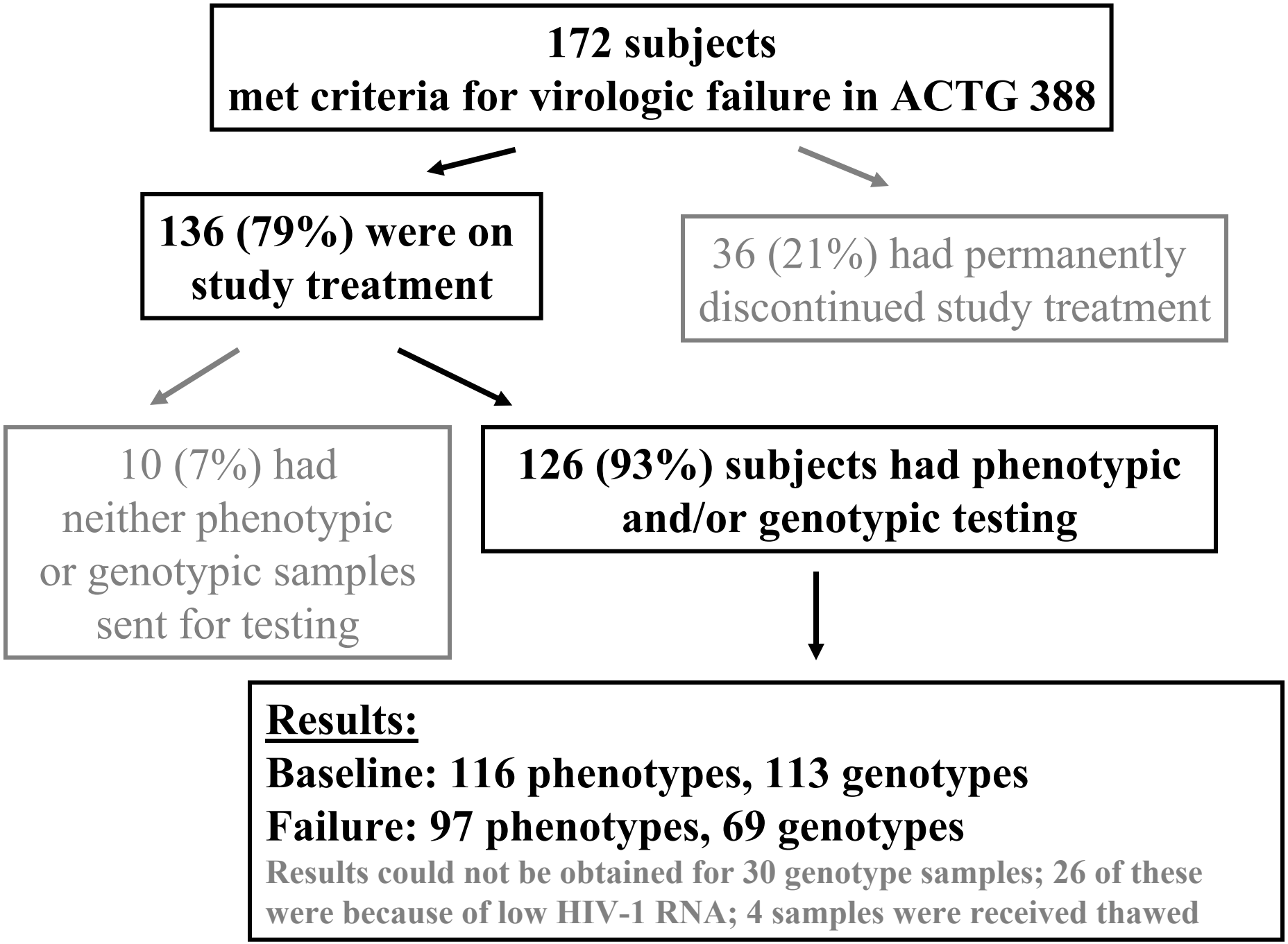
Introduction

- ACTG 388 was a randomized, open-label phase III clinical trial in subjects with advanced HIV disease
  - Oral abstract 40-T, Fischl *et al.*
- Subjects were randomized to receive
  - 3TC/ZDV+IDV
  - 3TC/ZDV+IDV+EFV
  - 3TC/ZDV+IDV+NFV
- To determine the relationship of drug resistance to virologic failure in ACTG 388, we analyzed the phenotype and genotype of HIV-1 in samples collected at baseline and at the time of virologic failure from participants meeting the criteria for virologic failure

Methods

- **Phenotypic Resistance Testing**
  - Measured using a commercial recombinant virus assay (PhenoSense, ViroLogic Inc., South San Francisco, CA).
  - Definition of resistance: $IC_{50} \geq$ 3-fold higher than the reference strain for each drug
- **Genotypic Resistance Testing**
  - Performed at three AACTG laboratories using the Applied Biosystems HIV-1 Genotyping System (version 1.0).
  - Resistance mutations were defined according to the IAS-USA Update on Drug Resistance Mutations in HIV-1 (http://www.iasusa.org).
- **Restrictions in resistance data collection**
  - Resistance was only studied in subjects meeting the criteria for virologic failure.
  - Subjects who had discontinued study treatment at the time of failure were excluded (resistance information maybe misleading in this situation due to reemergence of wild-type virus).

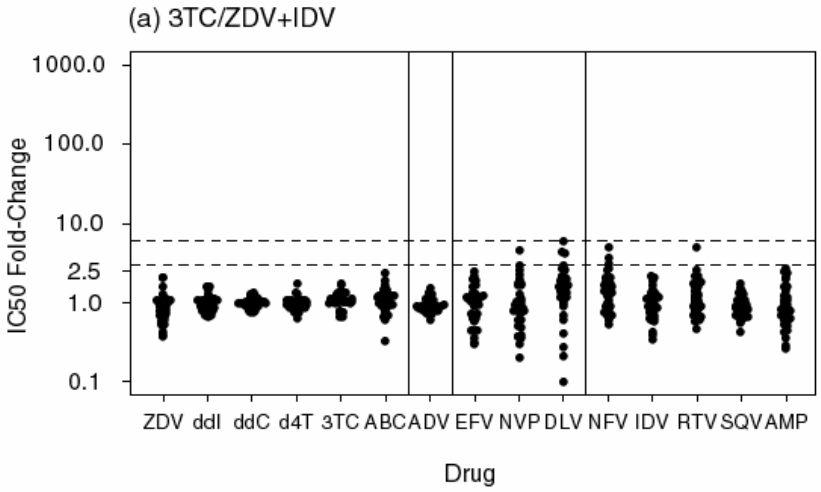

172 subjects
met criteria for virologic failure in ACTG 388
136 (79%) were on study treatment
36 (21%) had permanently discontinued study treatment
10 (7%) had neither phenotypic or genotypic samples sent for testing
126 (93%) subjects had phenotypic and/or genotypic testing
Results:
Baseline: 116 phenotypes, 113 genotypes
Failure: 97 phenotypes, 69 genotypes
Results could not be obtained for 30 genotype samples; 26 of these were because of low HIV-1 RNA; 4 samples were received thawed

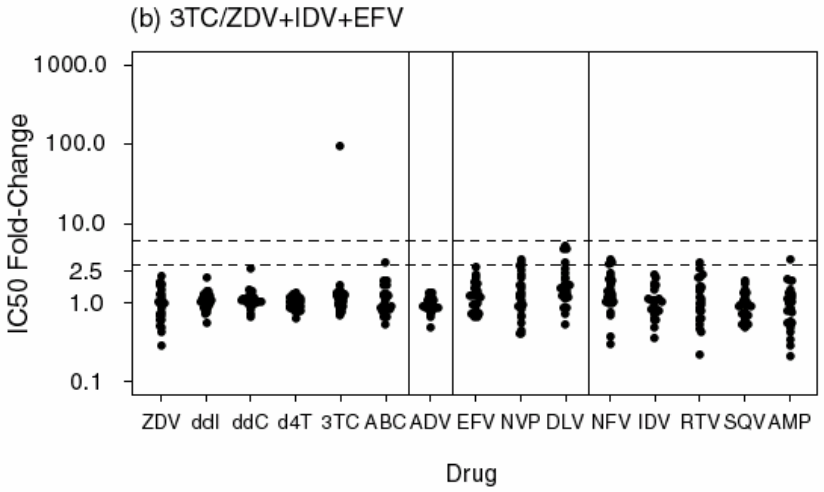
Baseline Characteristics of Study Subjects

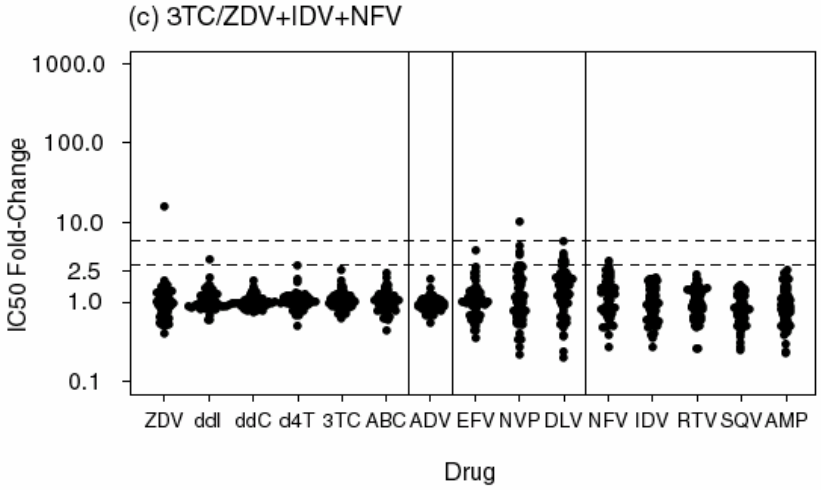
Age (years)	Mean (sd)	36.1 (7.8)
Gender	Men Women	82% 18%
Treatment arm	3TC/ZDV + IDV 3TC/ZDV + IDV+EFV 3TC/ZDV + IDV+NFV	31% 21% 48%
Prior nRTI therapy	None Some	87% 13%
CD4 cell count (cells/mm^3)	Mean (sd)	143 (143)
HIV-1 RNA ($\log_{10}$ copies/ml)	Mean (sd)	5.40 (0.56)

There were no significant differences between the subjects with virologic failure who were included and those who were excluded from the study.

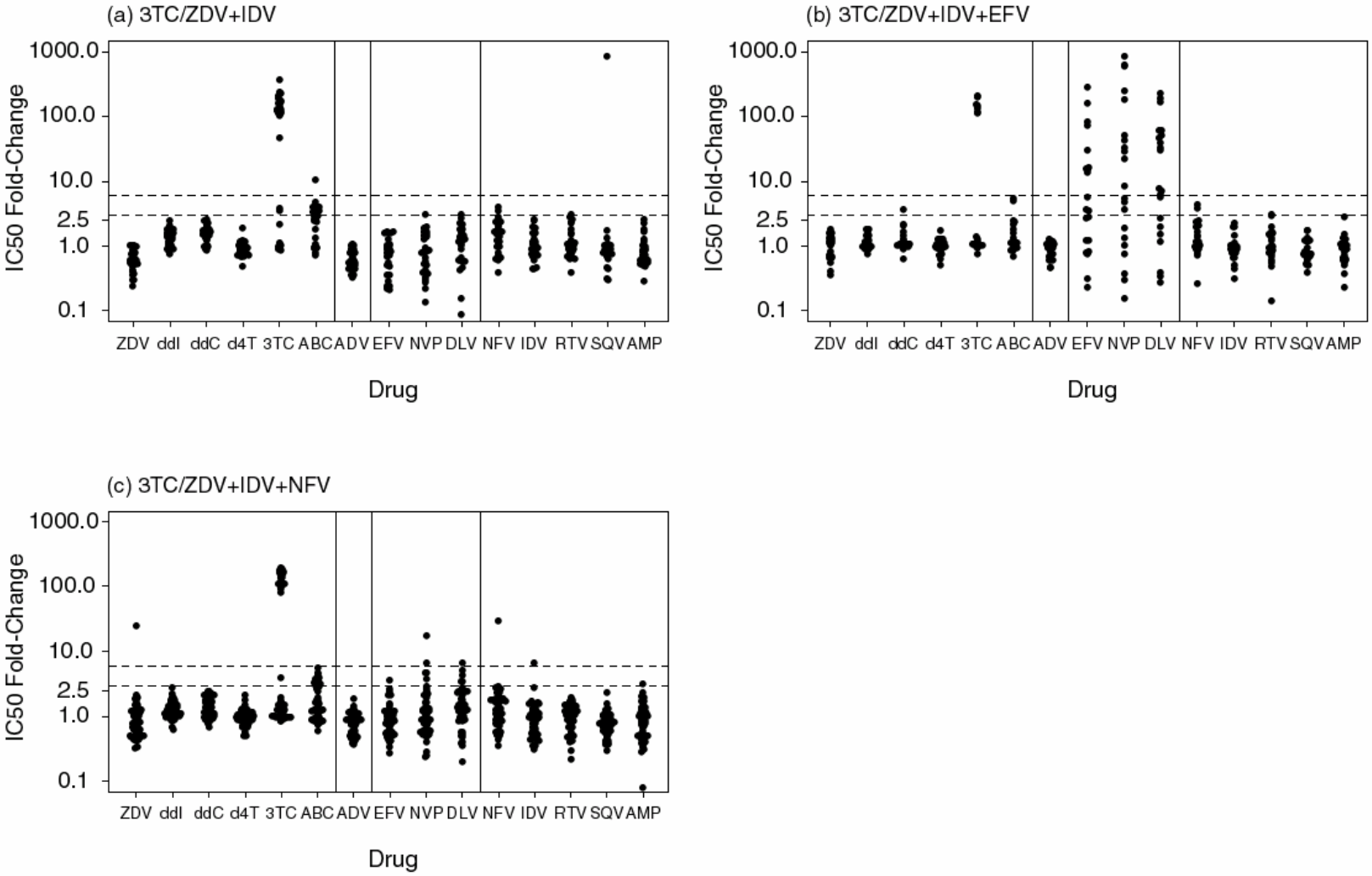
IC50 Fold Change at baseline by drugs and treatment arm



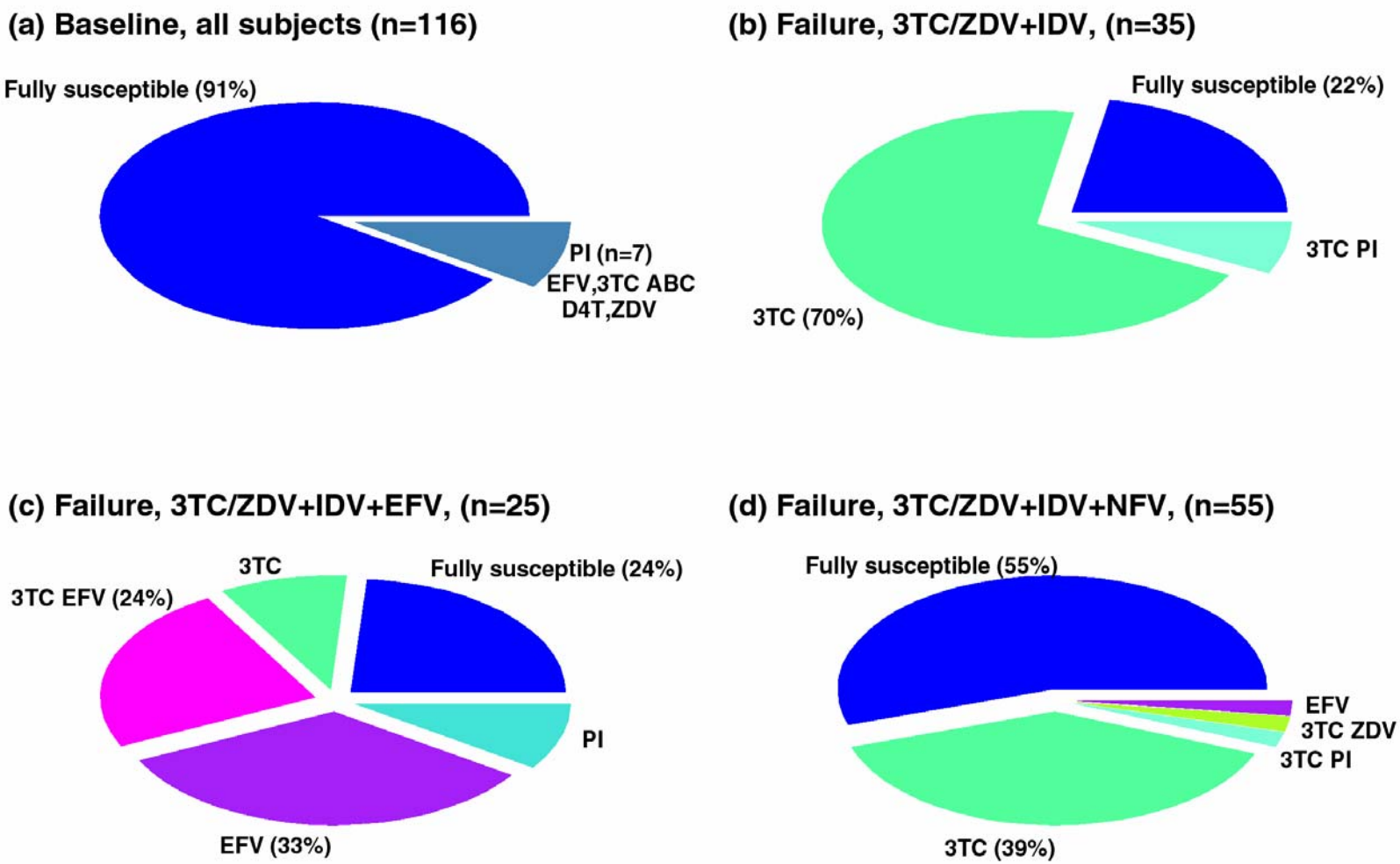




IC50 Fold Change at failure by drug and treatment arm



Phenotypic Resistance at Baseline and at Virologic Failure



Phenotypic Resistance at Failure

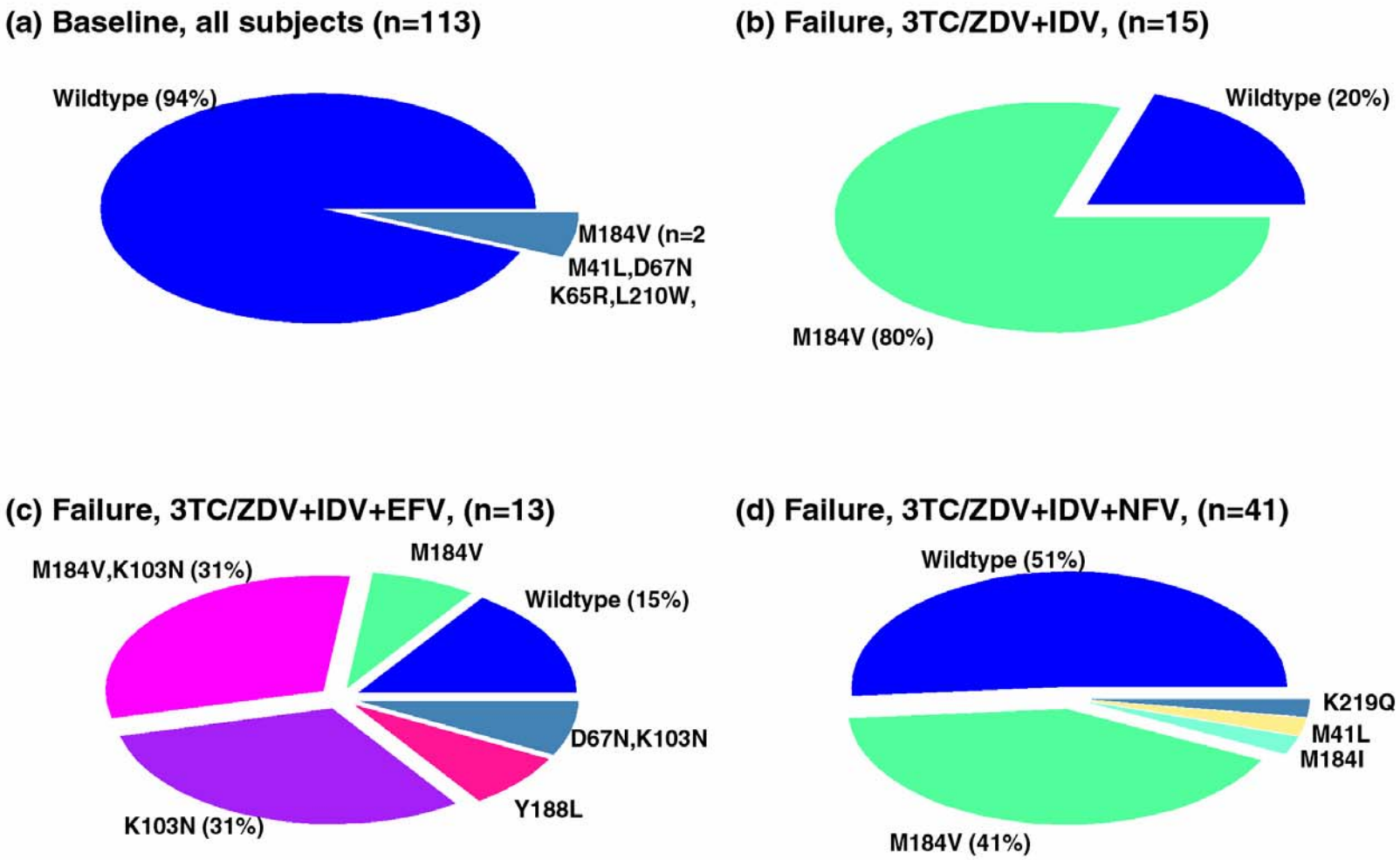
	IDV	IDV+EFV	IDV+NFV
Fully Susceptible	6 (22%)	5 (24%) *P=0.90**	27 (55%) *P=0.006**
Resistant to 3TC	21 (78%)	7 (33%) *P=0.002**	21 (43%) *P=0.003**

Chi-square test, compared to IDV arm

- **HIV-1 resistant to EFV was found in 13 (13%) subjects at failure; 12 of these subjects were in the IDV+EFV arm; a wildtype genotype was observed for the 1 subject in the IDV+NFV arm**

- **Five (5%) subjects harbored HIV-1 with a protease-resistant phenotype at failure; 3 of these subjects had a virus susceptible to protease inhibitors at baseline; all of these subjects had a wildtype genotype.**

Genotypic Resistance at Baseline and at Virologic Failure



Genotypic Resistance at Failure
Phenotypic Resistance to Study Drugs in Early and Late Virologic Failure

RT sequence	IDV	IDV+EFV	IDV+NFV
Wild-type	3 (20%)	2 (15%) *P=0.67**	21 (51%) *P=0.04**
Mutations at position 184	12 (80%)	5 (38%) *P=0.03**	18 (44%) *P=0.02**

Chi-square test, compared to IDV arm

- Mutations at position 103 and/or 188 were found in 10 subjects, all in the IDV+EFV arm.

- Secondary protease resistance mutations remained largely unchanged from baseline.

Phenotypic Resistance to Study Drugs in Early and Late Virologic Failure

	IDV		IDV+EFV		IDV+NFV	
	Early	Late	Early	Late	Early	Late
Fully susceptible	3 (21%)	3 (23%)	3 (18%)	4 (40%)	18 (62%)	9 (45%)
3TC	11 (79%)	8 (77%)	0	1 (10%)	10 (35%)	10 (50%)
3TC/ZDV	0	0	0	0	1 (3%)	0
EFV	0	0	6 (55%)	1 (10%)	0	1 (5%)
3TC/EFV	0	0	1 (9%)	4 (40%)	0	0
Fisher's exact test	*P=1*		*P=0.09*		*P=0.33*	

Note: Early and late failure were defined as confirmed virologic failure occurring before and after week 24, respectively.

Discussion

- At failure, HIV-1 with a resistant phenotype was present in 61% of the subjects, and HIV-1 with a resistant genotype was found in 62% of the subjects.

- 3TC-resistant HIV-1 was the most common virus found across all study arms at failure.

- At failure, HIV-1 with an EFV-resistant phenotype or genotype was present in 57% and 77% of the subjects in the EFV arm, respectively.

- Multiclass resistance was infrequent and only found at failure in the EFV arm.

  Note: Virologic failure was less common in the EFV arm (a failure probability of 22% at 96 weeks)

Discussion (Continued)

- Drug-sensitive HIV-1 was more common at failure in the NFV arm, suggesting other factors as the cause of virologic failure in this group.

- This study found low frequencies of phenotypic and genotypic antiretroviral resistance at baseline among antiretroviral naïve subjects.

- Resistance to protease inhibitors was uncommon, suggesting that the antiretroviral combinations used in ACTG 388 could delay the emergence of HIV-1 resistant to these compounds.