



Selection of Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Resistant HIV-1 After Discontinuation of a Virologically Suppressive Regimen

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Background

- Patients may discontinue virologically suppressive antiretroviral therapy (ART) regimens for reasons including patient choice or toxicity¹
- Upon ART discontinuation, drug-resistant virus may emerge as the predominant strain or as minor variants²
- The frequency of emergence and clinical significance of drug-resistant virus in this setting is undefined

¹ DHHS guidelines, May 4, 2006, <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

² Palmer and Coffin, AIDS 2006

Study Objectives

- Primary Objective:
 - To estimate the frequency of NNRTI resistance mutations among persons discontinuing virologically suppressive NNRTI-containing ART regimens
- Secondary Objectives:
 1. To determine the timing of emergence and persistence of NNRTI resistance mutations
 2. To identify predictors of resistance in this setting
 3. To assess the impact of detectable resistance on response to subsequent NNRTI treatment

Study Design

- Virologic Sub-study of ACTG A5170: Single-arm observational study of ART discontinuation with clinical and laboratory endpoints¹
- Inclusion criteria:
 - Nadir CD4 > 250; CD4 at enrollment > 350
 - On continuous ART for >6 months
 - Taking NNRTI at time of ART discontinuation
 - HIV RNA < 400 c/mL at entry
- Subjects instructed to discontinue NNRTI 2 days prior to other drugs

Methods

- Baseline resistance:
 - HIV DNA by Oligonucleotide Ligation Assay (OLA) from PBMC¹
- Resistance at viral rebound: (HIV RNA >5,000 c/mL)
 - Standard population-based genotype
 - If present, re-tested throughout period of study observation
 - Allele specific RT PCR for codons 103 and 181²
 - Tested only if standard genotype showed no resistance
- Pharmacokinetics:
 - NVP or EFV drug concentrations at baseline and Week-4 after treatment discontinuation, followed until undetectable
- Pharmacogenomics:
 - *CYP2B6* polymorphisms

1 Ellis and Frenkel, J Clin Micro 2004

2 Palmer and Coffin, AIDS 2006

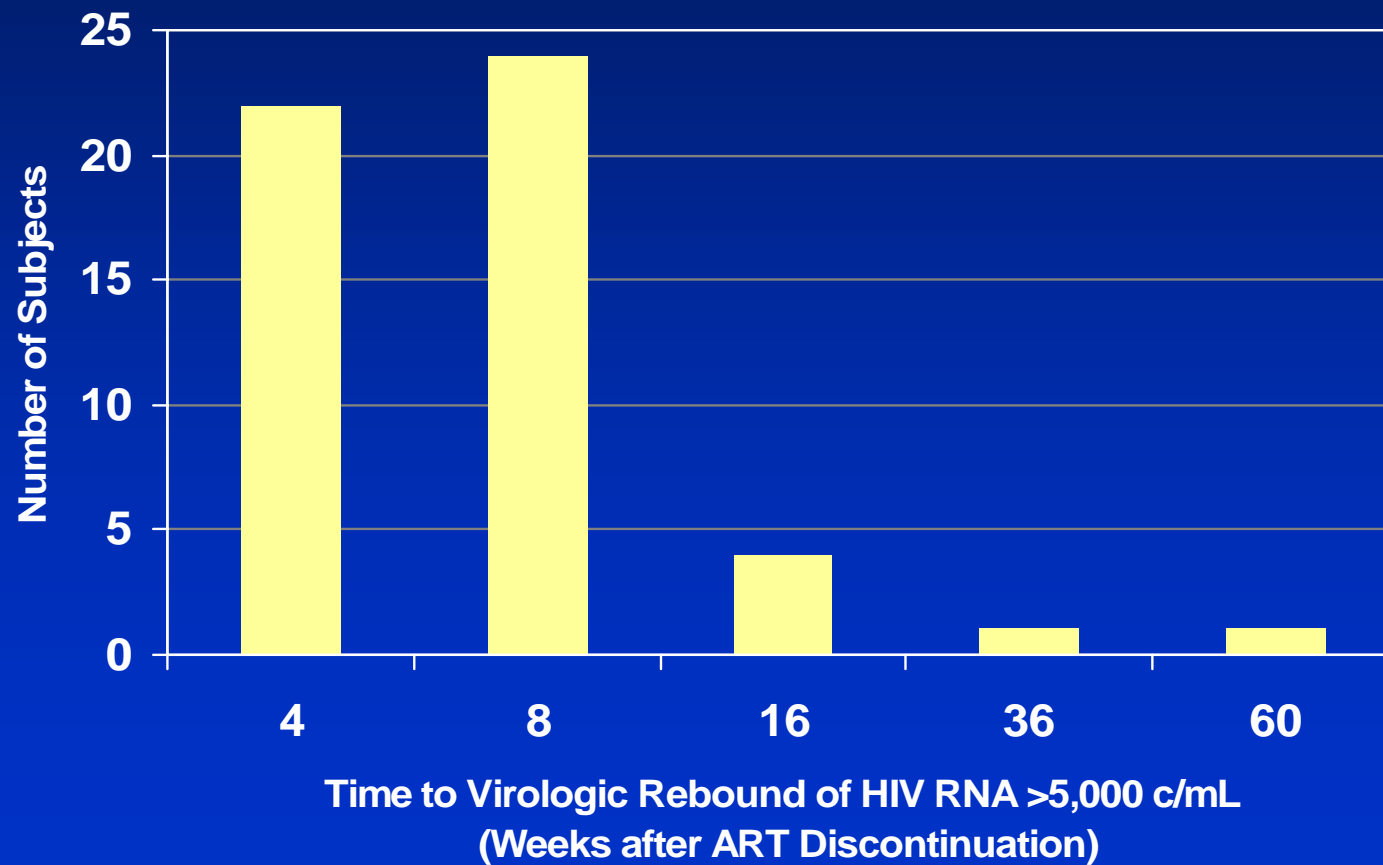
Subject Characteristics

	Total N = 54
Age, years (SD)	42.5 (8.8)
Gender, % male	85.2%
Race/ethnicity	
White	37 (68.5%)
Black	10 (18.5%)
Hispanic	5 (9.3%)
Other/unknown	2 (3.7%)
CD4 nadir prior to entry, cells/mL (SD)	458 (140)
CD4 at entry, cells/mL (SD)	873 (305)
Pre-Treatment HIV-1 RNA, log c/mL (SD)	4.6 (0.6)
HIV-1 RNA at entry, c/mL	
<=400	54 (100%)
<=50	43 (79.6%)
CYP2B6 genotype (N=45)	
GG	24 (44.4%)
GT	18 (33.3%)
TT	2 (3.7%)
failed assay	1 (2.2%)

Baseline ART History

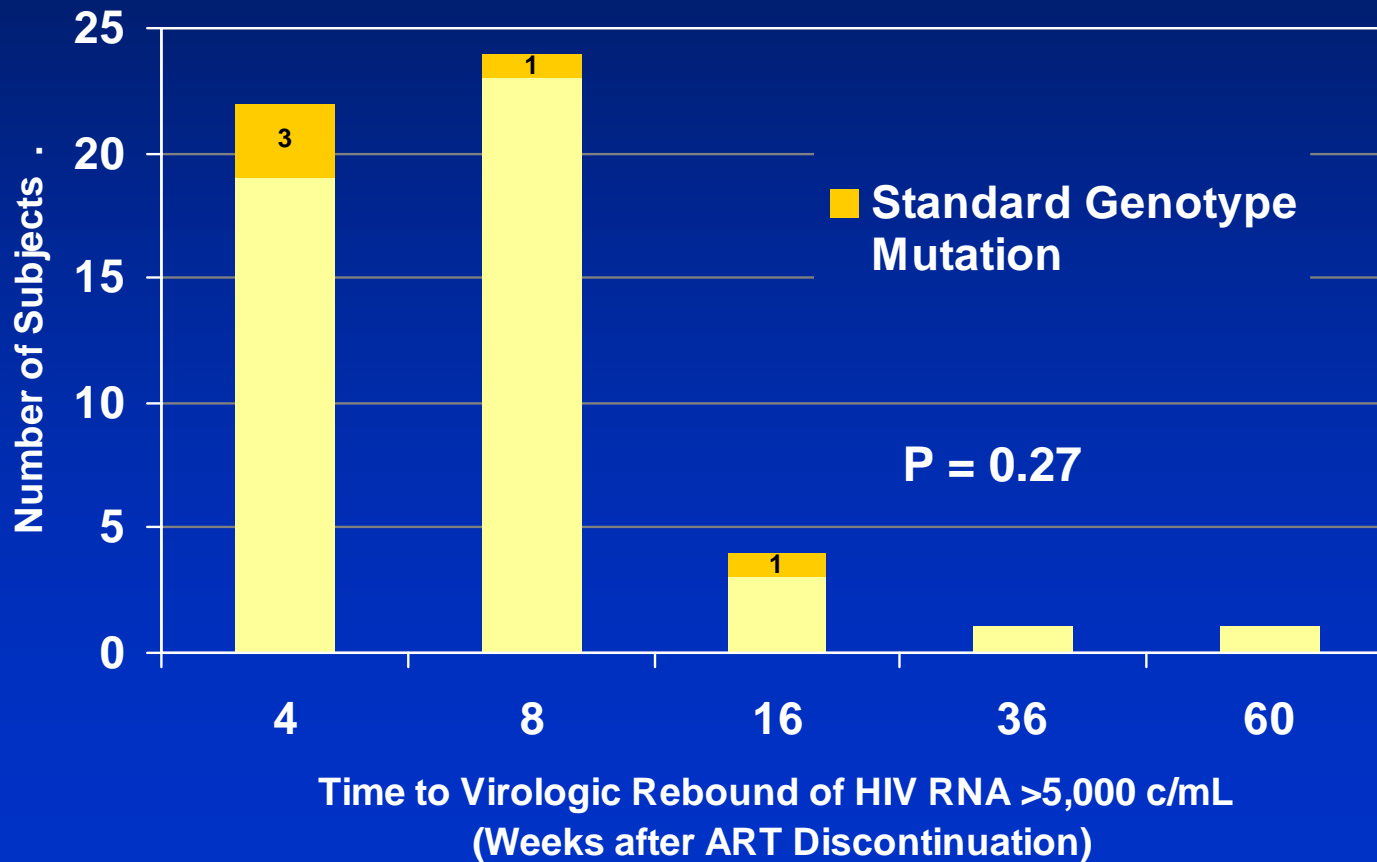
	Total N = 54
Baseline ART regimen	
Efavirenz (EFV)	33 (61.1%)
EFV + NRTIs only	31
EFV +NRTIs + PI	1
EFV + PI only	1
Nevirapine (NVP)	21 (38.9%)
NVP + NRTIs only	18
NVP + NRTIs + PI	3
Mean Duration of Baseline ART regimen in months (SD)	31.8 (18.1)
ART History	
Currently on first ART regimen	22 (40.7%)
Multiple prior ART regimens	32 (59.3%)

Time to Virologic Rebound



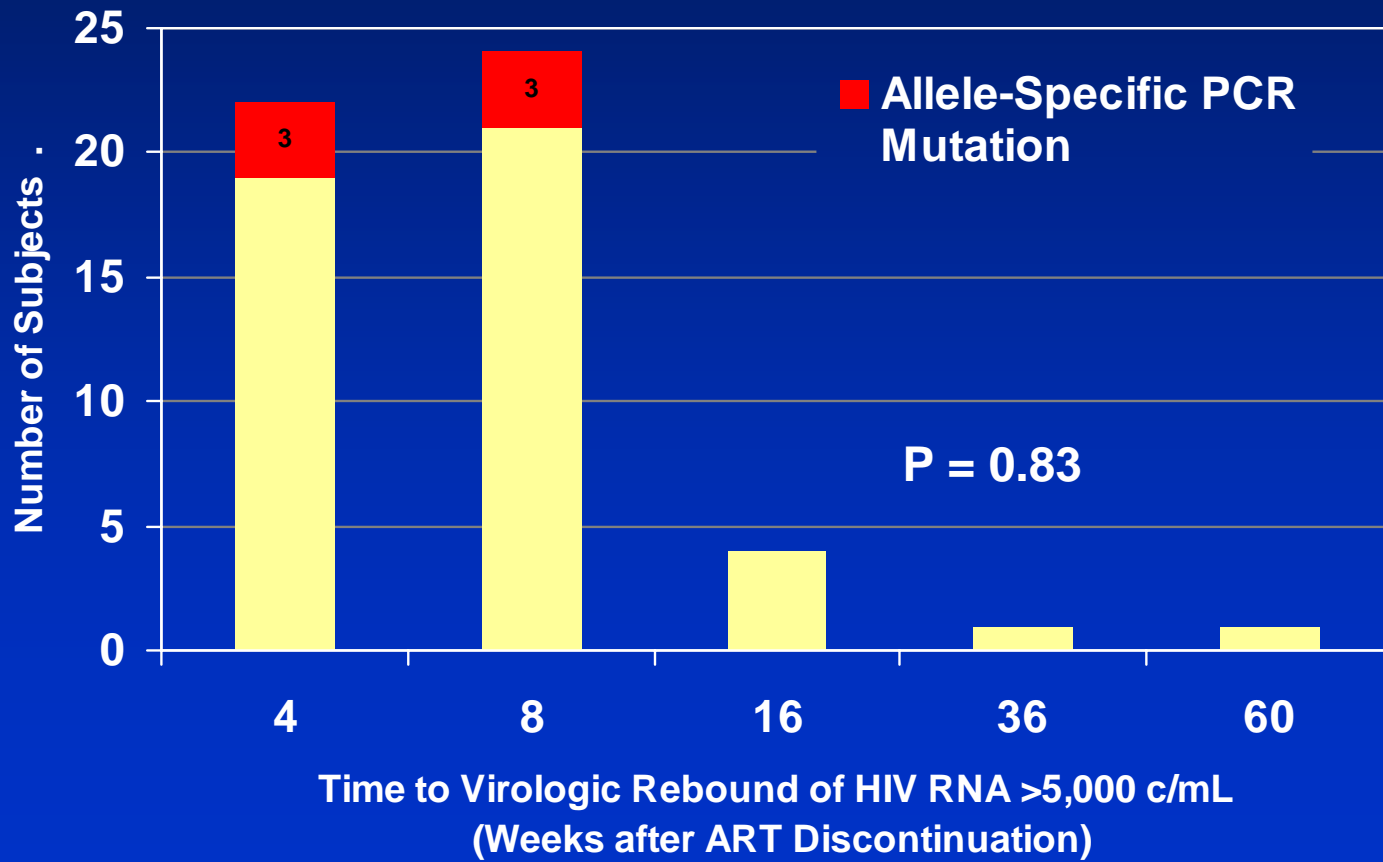
Standard Genotype Resistance

5/54 (9%) detectable resistance by Standard Genotype



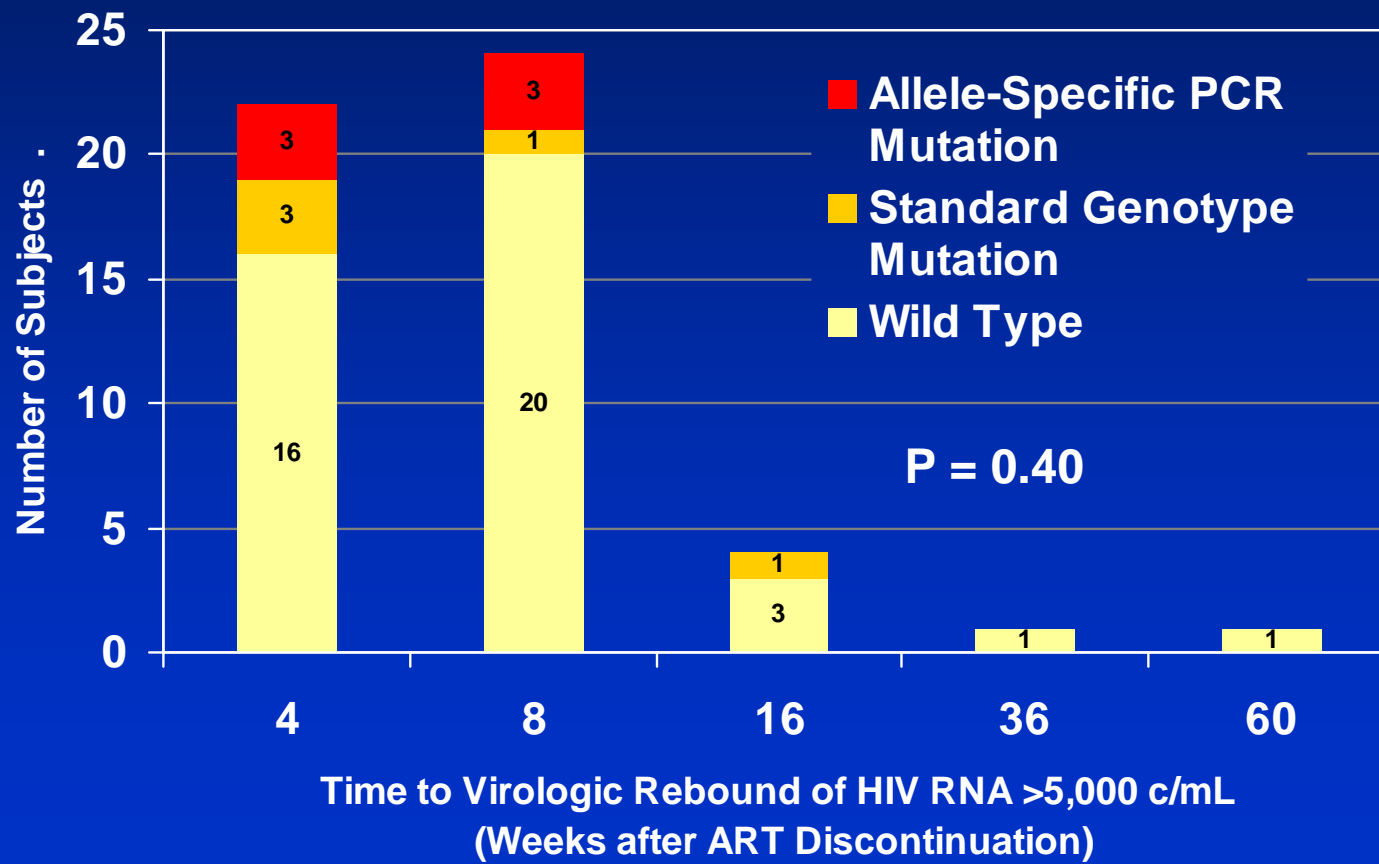
Allele-Specific PCR Resistance

6/54 (11%) detectable resistance by Allele-Specific PCR only



Resistance by Any Assay

TOTAL = 11/54 (20%) with detectable resistance by any assay



Drug Resistance Mutations at Baseline and Virologic Rebound

Subject ID	Baseline	Virologic Rebound	
	OLA	Standard Genotype	Allele Specific PCR (% mutant)
44627	K103N	K103N	--
212023	K103N	K103N	--
44768	G190A	K103N	--
291199	Wild type	K103N	--
373718	Wild type	K103N	--
72582	Wild type	Wild type	K103N (1.19%)
72710	Wild type	Wild type	K103N (0.25%)
83222	Wild type	Wild type	K103N (0.27%)
108037	Wild type	Wild type	K103N (0.51%)
291214	Wild type	Wild type	Y181C (0.47%)
320394	Missing	Wild type	K103N (2.11%) Y181C (0.26%)
520457	K103N	Wild type	Wild type
520729	K103N	Wild type	Wild type
272455	Y181C	Wild type	Wild type

Persistence of Resistance

- 5 subjects with resistance by Standard Genotype
 - All K103N
- 4 remained off ART for 36-48 weeks of follow-up
- 3 of the 4 subjects off ART had K103N detectable by standard genotype at their last determination prior to resuming ART (36-48 weeks off ART)

Predictors of Resistance

	Univariate Odds Ratio			Multivariate Odds Ratio
	Standard Genotype	Allele-Specific PCR	Any Assay	Any Assay
Baseline OLA Resistance*	22.0 2.7, 231 p=0.005	None	4.8 0.8, 30.2 p=0.08	2.6 0.3, 19.6 p=0.44
Baseline HIV RNA >50 c/mL*	27.0 3.4, 500 p=0.006	None	6.0 1.3, 28.6 p=0.02	3.8 0.7, 19.2 p=0.07

Data presented as Odds Ratios with 95% Confidence Intervals and P-values

*These two predictors were associated with each other, p=0.01, Fisher's exact test

Virologic Response After ART Re-Initiation

- 23 Subjects restarted ART during study observation
 - Restart with NNRTI, N = 18
 - Restart with exact same regimen, N = 13
- 5 Virologic failures observed
 - All failures among the N = 13 who started the exact same regimen
 - 2 failures had resistance by Standard Genotype prior to restarting ART (both K103N)
 - 3 failures had no resistance demonstrated prior to restarting ART

Summary

- Individuals who discontinue NNRTI-containing ART while virologically suppressed are at substantial risk (20%) of demonstrating NNRTI resistance at virologic rebound
- This resistance may persist for months in plasma by standard genotyping
- Resistance assays with increased sensitivity over standard genotyping may detect increased frequency of resistance
- The highest risk of resistance (45%) is associated with low-level viral replication (HIV RNA 51-400 c/ml) at treatment discontinuation

Implications

- Discontinuation of NNRTI regimens during periods of low-level viremia should be avoided
- Staggering NNRTI and non-NNRTI discontinuation by 2 days does not completely protect against resistance
- Genotype testing up to one year after NNRTI discontinuation may be of clinical utility
- The effect of this resistance on response to subsequent NNRTI-containing ART warrants further study

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Adult AIDS
Clinical Trials Group