

Low levels of adherence are associated with a higher proportion of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance than protease-inhibitor (PI) resistance

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Background

- Resistance to single protease inhibitor therapy occurs most frequently at high levels of adherence (1-5).
- The relationship between adherence and the risk of developing NNRTI resistance has not been well studied (7-9).

Hypothesis

- NNRTI resistance will occur at lower levels of adherence than single (“non-boosted”) PI resistance because:
 - NNRTIs are potent and exert high selective pressure.
 - A single mutation is sufficient to cause high-level NNRTI resistance while multiple mutations are often necessary to cause high-level PI resistance.
 - NNRTIs act distant to the active site; resistance mutations therefore have limited impact on replicative capacity. In contrast, PIs act in the active site of the enzyme. Mutations to these drugs often dramatically affect replicative capacity.

Methods

- All participants were enrolled in the REACH study, a population-based cohort of urban poor HIV+ individuals in San Francisco who met the following eligibility criteria:
 - Stable NNRTI or single “non-boosted” PI therapy for >6 months.
 - Adherence measured with unannounced pill counts at their usual place of residence for a minimum of 12 months.
- Genotypic drug resistance was determined in all participants with HIV RNA >50 copies/mL.
- Resistance was defined as one or more major resistance mutations based on recent IAS USA guidelines.
- Participants whose viral load remained undetectable during the observation period were assumed to have not developed drug-resistance.
- The association between adherence quartile and PI or NNRTI resistance was tested with chi square for trend and logistic regression.

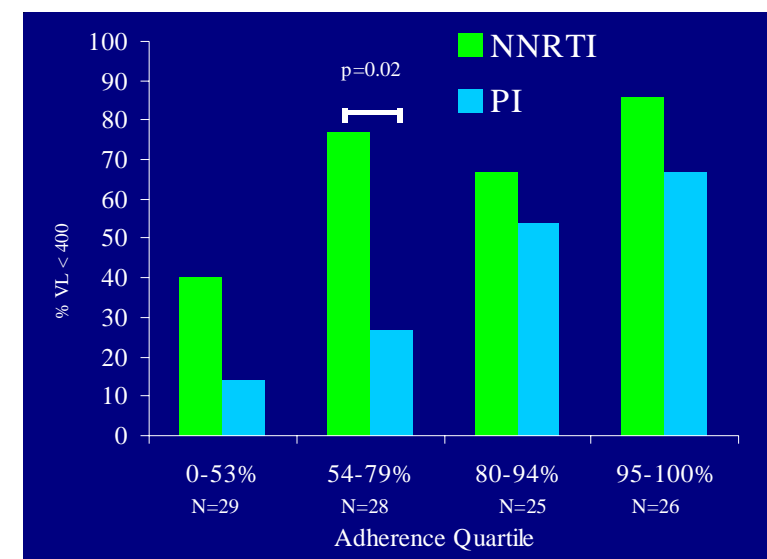
Results

- Of 108 eligible participants, 72 (66%) had detectable viremia and 36 (34%) were fully suppressed during the observation period.
 - 54 individuals received an NNRTI-based regimen.
 - 54 received a PI-based regimen.
- Prevalence of resistance:
 - 21 of 54 (38%) NNRTI treated individuals had NNRTI resistance.
 - 15 of 54 (27%) PI treated individuals had PI resistance.

Table 1. Demographic and Treatment Characteristics

	NNRTI N=54	PI N=54	Total N=108	p-value
Age (median)	41	46	44	0.09
Male (%)	87%	83%	85%	0.79
Race (% nonwhite)	50%	66%	58%	0.12
Months prior HAART (median)	24.5	16.0	20.0	0.87
Months on regimen (median)	9	10.5	9.5	0.40
Ever IDU	61%	56%	58%	0.70
Homeless (living on street or in a shelter)	28%	18%	23%	0.36
Prior mono/dual nucleoside exposure (%)	35%	48%	42%	0.24
ARV naïve (%)	24%	15%	19%	0.33
CD4/ml nadir (median)	192	236	214	0.10
Adherence (median)	73%	71%	72%	0.59
NNRTI Distribution (N=54)				
Efavirenz	35%		18%	
Nevirapine	65%		32%	
PI Distribution (N=54)				
Nelfinavir		63%	31%	
Indinavir		28%	14%	
Saquinavir		7%	4%	
Ritonavir		2%	1%	

Figure 1. Viral Suppression by Regimen and Adherence



	All	<80% Adherent	≥80% Adherent
NNRTI	67%	57%	60%
PI	39%	21%	56%

p=0.004 (NNRTI vs PI overall), p=0.007 (<80% Adherent), p=0.51 (≥80% Adherent)

Figure 2. Prevalence of Resistance by Regimen and Adherence

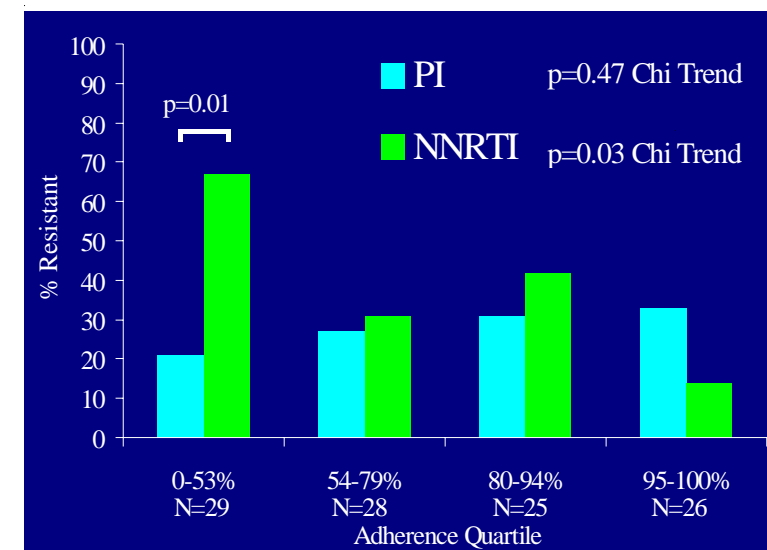


Table 2. Proportion of Wildtype Failure Among Individuals with VL>50

	Resistant	Wildtype
PI	15 (34%)	28 (65%)
NNRTI	21 (72%)	8 (23%)

p=.018

Table 3. Multivariable Analysis of NNRTI Resistance

Parameter	Adjusted Odds Ratio	95% Wald Confidence Limits		Pr > ChiSq
Adherence (+10%)	0.748	0.573	0.976	0.0324
Months on Regimen (+6 mo)	0.883	0.576	1.353	0.5673
Pre HAART mono/dual RTI	1.137	0.320	4.042	0.8431
CD4 nadir (+100 cells)	0.895	0.717	1.118	0.3274

Table 4. Multivariable Analysis of PI Resistance

Parameter	Adjusted Odds Ratio	95% Wald Confidence Limits		Pr > ChiSq
Adherence (+10%)	1.361	0.975	1.900	0.0703
Months on Regimen (+6 mo)	1.224	0.944	1.587	0.1274
Pre HAART mono/dual RTI	6.296	1.409	28.122	0.0160
CD4 nadir (+100 cells)	0.824	0.610	1.114	0.2090

Summary

- NNRTI regimens are associated with greater proportion of individuals with viral suppression than single PI regimens overall (p=0.004), and particularly at low-to-moderate levels (0-80%) of adherence (p=0.007; figure 1).
- NNRTI regimens are associated with a lower proportion of individuals with “wildtype failure” than single PI regimens (p=0.018; table 2).
- Among highly non-adherent individuals (< 50% of doses taken), the prevalence of resistance was higher in NNRTI than PI treated individuals (67% vs. 21%; p<0.01; figure 2).
- In a logistic model controlling for treatment duration, prior nucleoside exposure, and baseline CD4+ T cell count, the odds of NNRTI resistance declined with increasing adherence (OR=0.75 for a 10% increase in adherence p=.03; table 3).
- Conversely, there was a trend towards an increasing odds for PI resistance (OR=1.36 for a 10% increase in adherence; P=.07; table 4).

Conclusions

- NNRTIs are associated with higher rates of viral suppression, particularly at low levels of adherence, than single PI regimens.
- Resistance to NNRTI regimens is more common at low levels adherence compared to single PI regimens.
- The higher proportion of NNRTI resistance at low levels of adherence is due to lower proportion of individuals with “wild type failure.”
- Whereas low-pill burden NNRTI regimens are often advocated for patients at risk for nonadherence, these data suggest a tenuous balance between viral suppression and resistance in individuals with low levels of adherence to NNRTI regimens.

Limitations

- The primary outcome was the prevalence of mutations on stable therapy and may not reflect the evolution of new mutations on therapy.
- The treatment population was largely treatment experienced; results would likely differ in an exclusively treatment naïve population.
- Data was limited to single PI therapy. Adherence-resistance relationships are likely different for ritonavir-boosted PIs.

References

- Bangsberg D, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000, 14:357-366.
- Walsh JC, Pozniak AL, Nelson MR, Mandalia S and Gazzard BG. Virologic rebound on HAART in the context of low treatment adherence is associated with a low prevalence of antiretroviral drug resistance. *J Acquir Immune Defic Syndr* 2002; 30:278-87.
- Galleo O, de Mendoza C, Perez-Elias MJ, et al. Drug resistance in patients experiencing early virological failure under a triple combination including indinavir. *AIDS* 2001; 15:1701-6.
- Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS* 2003;17:1925-32.
- Miller L, McCutchan J, Keiser P, et al. Accumulation of Antiretroviral Resistance in Treatment-Experienced Patients: The Impact of Medication Adherence. In: XIIIth International HIV Drug Resistance Workshop. Los Cabos, Mexico, 2003.
- Bangsberg DR, Porco T, Kagay C, et al. Modeling the HIV protease inhibitor adherence-resistance curve using empirically derived estimates. *JID* 2004;(in press).
- Sethi AK, Celentano DD, Gange SJ, Moore RD and Gallant JE. Association between Adherence to Antiretroviral Therapy and Human Immunodeficiency Virus Drug Resistance. *Clin Infect Dis* 2003;37:1112-1118.
- Parienti J, Massari V, Descamps D, et al. Predictors of Virologic Failure and Resistance in HIV-Infected Patients Treated with Nevirapine or Efavirenz-Based Antiretroviral Therapy. *CID* 2004;38:1311-1316.
- Bangsberg DR, Moss AR and Deeks SG. Paradoxes of HIV antiretroviral adherence and drug resistance. *JAC* 2004;53: 696-9.

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