Analysis for the Resistance Collaborative Group

Association between phenotypic drug resistance and virologic response to mega-HAART regimen in patients from the Frankfurt HIV Cohort

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1. Introduction

This analysis was carried out in response to a request from the HIV Resistance Collaborative Group (RCG) as part of a series of exploratory analyses using a standardized data analysis plan (DAP) developed by the RCG to address the question of the utility of resistance testing in the clinical setting.

In this retrospective study, we have analyzed the association of baseline resistance as measured with a phenotypic assay and virologic response. Virologic response was defined as a reduction of plasma HIV RNA < 400 copies/ml, as measured by the Amplicor assay.

The study population consisted of patients from the Frankfurt HIV Out-Patient Clinic. In general, these patients had received extensive prior antiretroviral treatment.

All patients who had presented at least once since January 1, 1995, are included in the Frankfurt HIV Cohort database. This database contains prospectively collected information on patient demographics, antiretroviral treatment, CD4/CD8 status, viral load, HIV-1 drug resistance, use of OI prophylaxis, and clinical progression. In addition, serially collected plasma samples are available for restrospective in vitro investigations.

2. Methods

2.1 Patient selection and DAP requirements

We selected all patients from our cohort who started 6 or more antiretroviral agents simultaneously with sufficient follow-up (minimum of 24 weeks), with the required viral load data points and with a resistance test within 90 days of beginning mega-HAART. There were no other restrictions to the patient selection.

Information for the description of baseline characteristics was taken from our database. All previously taken antiretrovirals as well as the duration of each treatment have been documented, therefore an accurate medication history was available.

2.2 Phenotypic resistance

Phenotypic resistance was assessed using a recombinant virus based assay (Antivirogram™). Resistance was expressed as fold increase in IC50 compared with the wild-type control for each experiment. As requested by the DAP, two resistance-defining cut-offs were used: 4-fold and 10-fold.

2.3 Statistical Analysis

The DAP guidelines were followed closely. Patients were considered not to be on the original study regimen if they stopped all drugs, or if they added at least one new drug to the orignal mega-HAART regimen.

3. Results

3.1 Study Population

Out of 92 patients meeting the first selection criterion (starting $\geq$ 6 drugs simultaneously), 50 had viral load data points recorded within the window as required by the DAP as well as a complete resistance test prior to starting mega-HAART.

The baseline characteristics are described in Table 1. The patient population was relatively advanced (median CD4 cell count: 95 cells/μl) with a median viral load of 5.52 log10 copies/ml. Pre-treatment was extensive, with a median time on HAART of 18 months.

Table 2 shows the previous antiretroviral treatments received. The patient population was heavily pre-treated in all three drug classes. The treatment history reflects the calendar time of the treatments, with very few patients (94%) having been exposed to Abacavir for more than one week, whereas all patients had received lamivudine for more than one week. The patient population had no previous exposure to delavirdine, efavirenz, saquinavir (soft-gel) nor amprenavir.

3.2 Treatment regimen

Table 3 lists the treatment regimen received during follow-up. 90% of patients received 6 or 7 drugs, and 10% received at least 8. 100% of patients received NRTIs and PIs, and 60% also received an NNRTI as part of their mega-HAART regimen.

3.3 Baseline phenotypic resistance

Resistance at baseline was extensive. 57% of patients had virus populations resistant to at least two NRTIs, and 66% of the patients had viruses resistant to at least two NNRTIs.

3.4 Virologic Endpoints

Using the DAP definitions, 39 patients experienced virologic failure (DAF analysis). For the DAC analysis, 8 patients were censored and 31 patients experienced virologic failure.

3.5 Logistic Regression Models

The results of the logistics regression models are presented in Table 4 (DAF analysis) and Table 5 (DAC analysis). In each table, the univariate model results are listed along with four different multivariate models.

Using the DAF plan (Table 4), the univariate model showed that baseline viral load was associated with an increased risk of failure wheras the total number of drugs to which the virus population retained susceptibility (4-fold AND 10-fold cut-off), was associated with a significantly reduced risk of failure. When looking at susceptibility

to the individual drug classes, sensitivity to protease inhibitors, but not NRTIs was associated with reduced risk of failure. Very similar results were obatined using the DAC plan (Table 5), with baseline viral load showing a trend for increased risk. Number of new drugs started was not associated with failure using either analysis plan.

Multivariate 1 (Viral load, number of new drugs, total number drugs susceptible to -- 4-fold cut-off)

In this model, using the DAF plan only baseline viral load (OR: 4.00, 95% CI: 1.19-13.48) and total number of drugs to which the virus retained susceptibility (OR: 0.35, 95% CI: 0.18-0.69) were significantly associated with failure. Very similar results were obtained using the DAC plan.

Multivariate 2 (Viral load, number of new drugs, total number drugs susceptible to-- 10-fold cut-off)

Both DAF and DAC plans yielded results very similar to the results using a 4-fold cut-off.

Multivariate 3 (Viral load, number of new drugs, number of PIs and number of NRTIs to which the virus population retained susceptibility – 4-fold cut-off)

Both DAF and DAC showed that only the number of PIs to which the virus population was sensitive was significantly associated with failure

Multivariate 4 (Viral load, number of new drugs, number of PIs and number of NRTIs to which the virus population retained susceptibility — 10-fold cut-off)

Both DAF and DAC analysis plans yielded results that were fully consistent with the 4-fold cut-off analysis.

4. Discussion

This analysis, although based on a relatively small patient population, indicates that phenotypic resistance testing yields useful information for predicting virological response that is independent of knowledge of treatment history. These results were obtained from a very extensively pre-treated patient population from a clinical setting, rather than a clinical trial. Thus there were no restrictions with regard to antiretroviral pre-treatment, nor restrictions with regard to which drugs could or could not be used in the salvage regimen. Therefore, these patients represent those with multiple therapy failure and multi-drug resistance that represent the "hard-to-treat" patient population presenting in many clinics and indicate that the use of resistance testing may assist in the choice of more effective follow-up multi-drug combination treatment.

Whether phenotype or genotype yields more useful results could not be analyzed with the data presently available, but will be the subject of future studies.

TABLES

Table 1
Study population: baseline characteristics

Characteristic	Median	Range
HIV RNA log10 copies/mL	5.52	3.40-6.70
CD4 count cells/mm3	95	2-587
Time on HAART months	18.3	1.7-53.5

Table 2
Summary of previous ART*

	< 1 week		1 week-1year		> = 1 year	
Drugs	***n***	***%***	***n***	***%***	***n***	***%***
Zidovudine	2	4.0	10	20.0	38	76.0
Zalicitabine	21	42.0	22	44.0	7	14.0
Didanosine	16	32.0	23	46.0	11	22.0
Stavudine	5	10.0	27	54.0	18	36.0
Lamivudine	0	0.0	13	26.0	37	74.0
Abacavir	47	94.0	3	6.0	0	0.0
Loviride	44	88.0	1	2.0	5	10.0
Tivirapine	49	98.0	1	2.0	0	0.0
Nevirapine	17	34.0	30	60.0	3	6.0
Saquinavir	14	28.0	28	56.0	8	16.0
Indinavir	13	26.0	28	56.0	9	18.0
Ritonavir	22	44.0	20	40.0	8	16.0
Nelfinavir	33	66.0	17	34.0	0	0.0
HAART	0	0.0	5	10.0	45	90.0

*no previous exposure to delaviridine, efavirenz, saquinavir (soft-gel), and amprenavir in this patient population

Table 3
Drugs received in the original mega-HAART regimen

	n	%
no of drugs		
6	27	54.0
7	18	36.0
8	4	8.0
9	1	2.0
Drugs		
Zidovudine	24	48.0
Zalicitabine	11	22.0
Didanosine	42	84.0
Stavudine	22	44.0
Lamivudine	50	100.0
Abacavir	11	22.0
Delaviridine	5	10.0
Nevirapine	24	48.0
Efavirenz	1	2.0
Saquinavir		
hard gel	20	40.0
soft gel	6	12.0
Indinavir	24	48.0
Ritonavir	47	94.0
Nelfinavir	42	84.0
PI	50	100.0
NNRTI	30	60.0

Table 4
Odds ratios of virological failure from fitting the logistic regression (DAF analysis)
39 failures out of 50 patients included (78.0%)

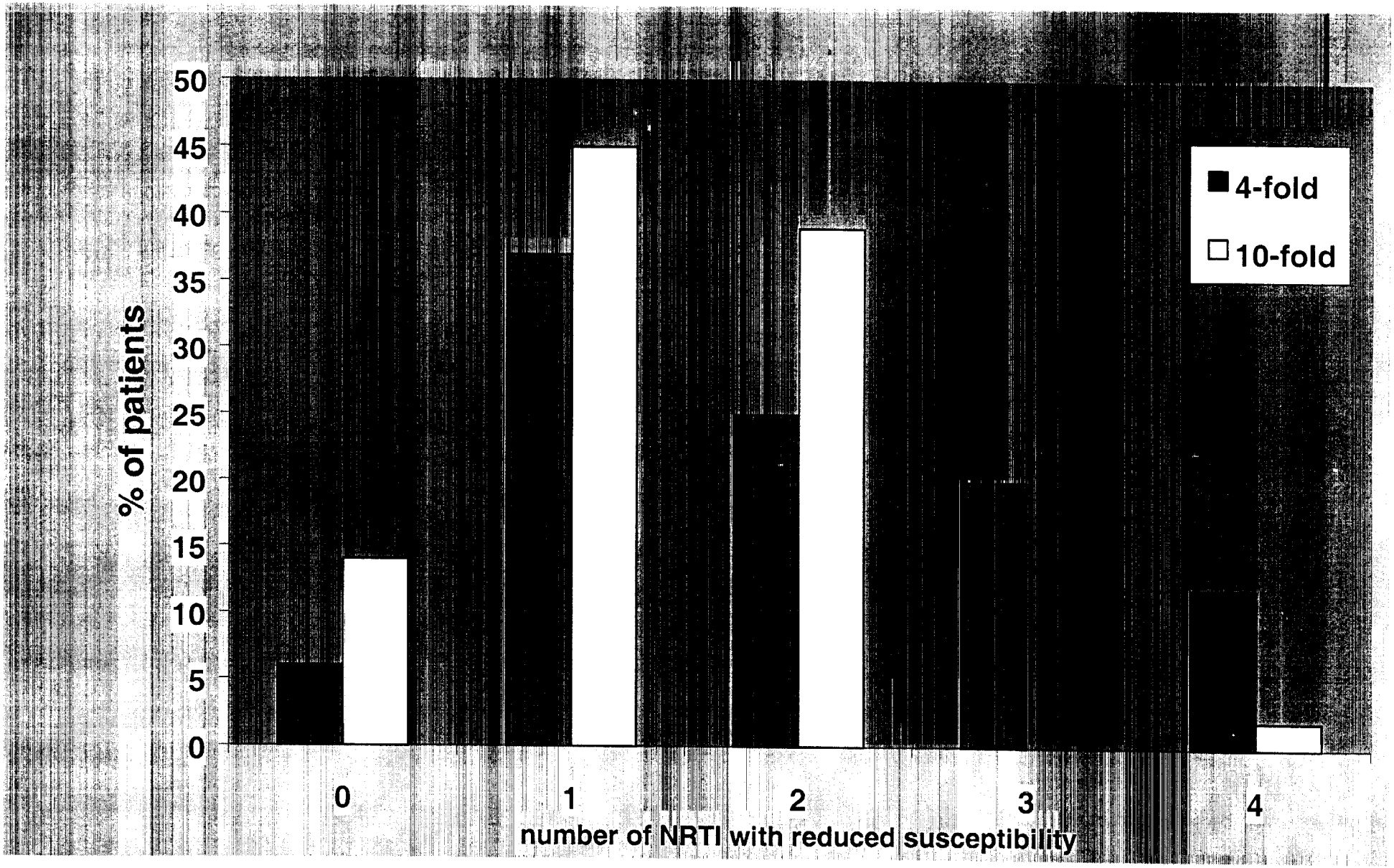
	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*
HIV RNA log10 higher	2.17 (1.00-4.73) p=0.05	4.00 (1.19-13.48) p=0.03	3.10 (1.10-8.74) p=0.03	1.91 (0.75-4.84) p=0.17	1.97 (0.82-4.73) p=0.13
New drugs started 1 extra drug	0.84 (0.52-1.36) p=0.47	1.18 (0.62-2.23) p=0.62	0.97 (0.54-1.75) p=0.93	1.02 (0.58-1.79) p=0.95	1.00 (0.58-1.72) p=0.99
no. of drugs susceptible to (cut-off=4) 1 extra drug	0.46 (0.28-0.74) p=0.002	0.35 (0.18-0.69) p=0.003			
no. of drugs susceptible to (cut-off=10) 1 extra drug	0.47 (0.27-0.81) p=0.007		0.39 (0.19-0.77) p=0.007		
no. of NRTI susceptible to (cut-off=4) 1 extra drug	0.52 (0.19-1.39) p=0.19			0.60 (0.21-1.74) p=0.34	
no. of PI susceptible to (cut-off=4) 1 extra drug	0.55 (0.31-0.97) p=0.04			0.50 (0.27-0.94) p=0.03	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	0.74 (0.28-1.96) p=0.55				0.90 (0.31-2.57) p=0.84
no. of PI susceptible to (cut-off=10) 1 extra drug	0.43 (0.20-0.92) p=0.03				0.39 (0.17-0.90) p=0.03

Table 5
Odds ratios of virological failure from fitting the logistic regression (DAC analysis)
31 failures out of 42 patients included (73.8%), 8 censored

	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*
HIV RNA log10 higher	2.05 (0.94-4.46) p=0.07	3.83 (1.17-12.57) p=0.03	2.91 (1.06-8.04) p=0.04	1.89 (0.76-4.72) p=0.17	1.91 (0.80-4.54) p=0.15
New drugs started 1 extra drug	0.82 (0.51-1.33) p=0.43	1.07 (0.57-2.04) p=0.84	0.92 (0.51-1.65) p=0.78	0.97 (0.56-1.70) p=0.92	0.96 (0.56-1.65) p=0.89
no. of drugs susceptible to (cut-off=4) 1 extra drug	0.47 (0.29-0.77) p=0.003	0.37 (0.19-0.71) p=0.003			
no. of drugs susceptible to (cut-off=10) 1 extra drug	0.51 (0.29-0.87) p=0.01		0.42 (0.21-0.82) p=0.01		
no. of NRTI susceptible to (cut-off=4) 1 extra drug	0.56 (0.21-1.50) p=0.25			0.63 (0.22-1.86) p=0.41	
no. of PI susceptible to (cut-off=4) 1 extra drug	0.58 (0.33-1.02) p=0.06			0.53 (0.28-1.00) p=0.05	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	0.85 (0.33-2.19) p=0.74				1.02 (0.37-2.82) p=0.97
no. of PI susceptible to (cut-off=10) 1 extra drug	0.42 (0.19-0.94)				0.38 (0.15-0.94)

	p = 0.03				p = 0.04

Frankfurt [illegible] Cohort
Mega-HAART
October 99



Retrospective analysis of patients starting mega-HAART from the Frankfurt HIV Cohort

Summary: 29 September 1999

Patients were defined as receiving mega-HAART if they started 6 or more individual antiretroviral drugs simultaneously

50 patients matched the inclusion criteria required by DAP

On treatment definition: no longer on original study regimen if
1) stop ALL drugs
2) add one drug to the original mega-HAART regimen

Table 1
Study population: baseline characteristics

Characteristic	Median	Range
HIV RNA log10 copies/mL	5.51	3.40-6.70
CD4 count cells/mm3	93	2-587
Time on HAART Months	18.3	1.7-53.5

Table 2
Summary of previous ART*

	<1 week		1 week-1year		> = 1 year	
Drugs	***n***	***%***	***n***	***%***	***n***	***%***
Zidovudine	2	4.0	9	18.0	39	78.0
Zalicitabine	22	44.0	21	42.0	7	14.0
Didanosine	16	32.0	22	44.0	12	24.0
Stavudine	5	10.0	27	54.0	18	36.0
Lamivudine	0	0.0	12	24.0	38	76.0
Abacavir	47	94.0	3	6.0	0	0.0
Loviride	44	88.0	1	2.0	5	10.0
Tivirapine	49	98.0	1	1.0	0	0.0
Nevirapine	18	36.0	29	58.0	3	6.0
Saquinavir	13	26.0	29	58.0	8	16.0
Indinavir	14	28.0	27	54.0	9	18.0
Ritonavir	21	42.0	21	42.0	8	16.0
Nelfinavir	34	68.0	16	32.0	0	0.0
HAART	0	0.0	6	12.0	44	88.0

no previous exposure to delaviridine, efavirenz, saquinavir (soft-gel), and amprenavir in this patient population

Table 3
Drugs received in the original mega-HAART regimen

	n	%
no of drugs		
6	28	56.0
7	17	34.0
8	4	8.0
9	1	2.0
Drugs		
Zidovudine	24	48.0
Zalicitabine	11	22.0
Didanosine	41	82.0
Stavudine	22	44.0
Lamivudine	50	100.0
Abacavir	11	22.0
Delaviridine	5	10.0
Nevirapine	24	48.0
Efavirenz	1	2.0
Saquinavir		
hard gel	19	38.0
soft gel	6	12.0
Indinavir	25	50.0
Ritonavir	47	94.0
Nelfinavir	42	84.0
PI	50	100.0
NNRTI	30	60.0

Table 4
Odds ratios of virological failure from fitting the logistic regression (DAF analysis)
40 failures out of 50 patients included (80.0%)

	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*
HIV RNA log10 higher	2.85 (1.19-6.83) p=0.02	5.27 (1.32-21.04) p=0.02	3.96 (1.24-12.57) p=0.02	2.46 (0.87-6.92) p=0.09	2.69 (1.01-7.19) p=0.05
New drugs started 1 extra drug	0.82 (0.50-1.36) p=0.44	1.12 (0.60-2.12) p=0.72	0.97 (0.54-1.75) p=0.92	1.01 (0.57-1.78) p=0.98	1.01 (0.58-1.78) p=0.96
no. of drugs susceptible to (cut-off=4) 1 extra drug	0.49 (0.30-0.79) p=0.004	0.36 (0.18-0.73) p=0.004			
no. of drugs susceptible to (cut-off=10) 1 extra drug	0.50 (0.29-0.87) p=0.01		0.41 (0.21-0.82) p=0.01		
no. of NRTI susceptible to (cut-off=4) 1 extra drug	0.35 (0.13-0.92) p=0.03			0.78 (0.25-2.42) p=0.67	
no. of PI susceptible to (cut-off=4) 1 extra drug	0.51 (0.32-0.84) p=0.008			0.49 (0.25-0.94 p=0.03	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	0.60 (0.22-1.63) p=0.31				1.25 (0.42-3.72) p=0.69
no. of PI susceptible to (cut-off=10) 1 extra drug	0.42 (0.20-0.88) p=0.02				0.38 (0.16-0.93) p=0.03

Table 5
Odds ratios of virological failure from fitting the logistic regression (DAC analysis)
32 failures out of 42 patients included (76.2%), 8 censored

	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*
HIV RNA log10 higher	2.66 (1.12-6.36) p=0.03	4.92 (1.28-18.96) p=0.02	3.64 (1.18-11.23) p=0.02	2.39 (0.87-6.61) p=0.09	2.57 (0.96-6.86) p=0.06
New drugs started 1 extra drug	0.81 (0.49-1.33) p=0.41	1.03 (0.54-1.95) p=0.94	0.92 (0.51-1.66) p=0.77	0.96 (0.54-1.69) p=0.88	0.96 (0.55-1.69) p=0.90
no. of drugs susceptible to (cut-off=4) 1 extra drug	0.51 (0.31-0.82) p=0.006	0.38 (0.19-0.75) p=0.005			
no. of drugs susceptible to (cut-off=10) 1 extra drug	0.54 (0.31-0.93) p=0.03		0.44 (0.22-0.87) p=0.02		
no. of NRTI susceptible to (cut-off=4) 1 extra drug	0.38 (0.14-0.99) p=0.05			0.82 (0.26-2.54) p=0.73	
no. of PI susceptible to (cut-off=4) 1 extra drug	0.55 (0.34-0.89) p=0.01			0.51 (0.26-1.00) p=0.05	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	0.68 (0.26-1.82) p=0.45				1.39 (0.47-4.09) p=0.56
no. of PI susceptible to (cut-off=10) 1 extra drug	0.43 (0.20-0.92) p=0.03				0.37 (0.14-0.98) p=0.05

Table 6
Mean change in HIV RNA (log10 copies/mL) by 4-12 weeks from fitting a linear regression model

	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*Mean change* *95% CI* *p-value*	*Mean change* *95% CI* *p-value*	*Mean change* *95% CI* *p-value*	*Mean change* *95% CI* *p-value*	*Mean change* *95% CI* *p-value*
New drugs started 1 extra drug	-0.16 (-0.45-+0.13) p=0.28	-0.07 (-0.37-+0.22) p=0.62	-0.10 (-0.38-+0.19) p=0.50	-0.14 (-0.44-0.16) p=0.36	-0.17 (-0.47-+0.13) p=0.26
Naïve to PI/NNRTI	+0.24 (-1.80-+2.30) p=0.81				
no. of drugs susceptible to (cut-off=4) 1 extra drug	-0.19 (-0.36-0.03) p=0.02	-0.18 (-0.35-0.01) p=0.04			
no. of drugs susceptible to (cut-off=10) 1 extra drug	-0.24 (-0.43-0.05) p=0.02		-0.23 (-0.22-0.03) p=0.03		
no. of NRTI susceptible to (cut-off=4) 1 extra drug	-0.33 (0.74-+0.08) p=0.11			-0.31 (0.73-+0.09) p=0.13	
no. of PI susceptible to (cut-off=4) 1 extra drug	+0.03 (-0.23-+0.30) p=0.80			+0.06 (-0.21-+0.32) p=0.68	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	-0.28 (-0.82-+0.26) p=0.31				-0.30 (-0.84-+0.24) p=0.27
no. of PI susceptible to (cut-off=10) 1 extra drug	-0.04 (-0.30-+0.23) p=0.78				-0.01 (-0.28-+0.26) p=0.95

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New drugs started 1 extra drug	0.82 (0.50-1.36) p=0.44	1.12 (0.60-2.12) p=0.72	0.97 (0.54-1.75) p=0.92	1.01 (0.57-1.78) p=0.98	1.01 (0.58-1.78) p=0.96
no. of drugs susceptible to (cut-off=4) 1 extra drug	0.49 (0.30-0.79) p=0.004	0.36 (0.18-0.73) p=0.004			
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no. of PI susceptible to (cut-off=4) 1 extra drug	0.51 (0.32-0.84) p=0.008			0.49 (0.25-0.94 p=0.03	
no. of NRTI susceptible to (cut-off=10) 1 extra drug	0.60 (0.22-1.63) p=0.31				1.25 (0.42-3.72) p=0.69
no. of PI susceptible to (cut-off=10) 1 extra drug	0.42 (0.20-0.88) p=0.02				0.38 (0.16-0.93) p=0.03

Table 5
Odds ratios of virological failure from fitting the logistic regression (DAC analysis)
32 failures out of 42 patients included (76.2%), 8 censored

	Univariate	Multivariate 1	Multivariate 2	Multivariate 3	Multivariate 4
Covariate	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*	*OR* *95% CI* *p-value*
HIV RNA log10 higher	2.66 (1.12-6.36) p = 0.03	4.92 (1.28-18.96) p = 0.02	3.64 (1.18-11.23) p = 0.02	2.39 (0.87-6.61) p = 0.09	2.57 (0.96-6.86) p = 0.06
New drugs started 1 extra drug	0.81 (0.49-1.33) p = 0.41	1.03 (0.54-1.95) p = 0.94	0.92 (0.51-1.66) p = 0.77	0.96 (0.54-1.69) p = 0.88	0.96 (0.55-1.69) p = 0.90
no. of drugs susceptible to (cut-off = 4) 1 extra drug	0.51 (0.31-0.82) p = 0.006	0.38 (0.19-0.75) p = 0.005			
no. of drugs susceptible to (cut-off = 10) 1 extra drug	0.54 (0.31-0.93) p = 0.03		0.44 (0.22-0.87) p = 0.02		
no. of NRTI susceptible to (cut-off = 4) 1 extra drug	0.38 (0.14-0.99) p = 0.05			0.82 (0.26-2.54) p = 0.73	
no. of PI susceptible to (cut-off = 4) 1 extra drug	0.55 (0.34-0.89) p = 0.01			0.51 (0.26-1.00) p = 0.05	
no. of NRTI susceptible to (cut-off = 10) 1 extra drug	0.68 (0.26-1.82) p = 0.45				1.39 (0.47-4.09) p = 0.56
no. of PI susceptible to (cut-off = 10) 1 extra drug	0.43 (0.20-0.92) p = 0.03				0.37 (0.14-0.98) p = 0.05