Resistance Collaborative Group Analysis

The Predictive Quality of Genotype and Phenotype Data On Virologic Failure in HIV-1 Infected Subjects Who Had Failed a Protease Inhibitor Regimen (CNAA2007)

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1. INTRODUCTION

The HIV Resistance Collaborative Group (RCG) requested an exploratory, retrospective analysis using the RCG standardized data analysis plan (DAP) to ascertain the utility of resistance testing in clinical trials. This report addresses the association of baseline resistance information with a virologic endpoint (i.e., reduction of plasma HIV RNA < 400 copies/mL via Amplicor assay) in a Glaxo Wellcome sponsored clinical trial CNAA2007. The study population being re-analyzed consists of heavily pretreated HIV-infected subjects who were being treated with abacavir (ABC) + amprenavir (APV) + efavirenz (EFV). Genotypic and phenotypic information were available for both reverse transcriptase and protease coding regions.

2. METHODS

2.1. Study Design

CNAA2007 was a phase II, open-label, single-arm, multi-center study of approximately 100 HIV-1 infected subjects to evaluate the safety and antiviral activity of combination therapy with ABC, APV and EFV in subjects with screening HIV-1 plasma RNA levels of ≥500 copies/mL despite at least 20 weeks treatment with at least one of the following PIs: indinavir, ritonavir, saquinavir and/or nelfinavir. There were no CD4+ cell count restrictions. Subjects must have been receiving combination therapy including at least one of the PIs listed above, at screening and up to study entry, and have been receiving the same PI therapy during the most recent 12 weeks. All subjects were required to stop all background antiretroviral agents at study entry (Day 1) and switch to the combination of ABC 300 mg BID, APV 1200 mg BID and EFV 600 mg QD. Subjects who were unable to be treated with one of the investigational agents due to toxicity or intolerance during the first 16 weeks on study were allowed to be treated with additional antiretroviral therapy after discussion of options and agreement between the coordinating investigator (at NIH), the sponsors of the study and the principal investigator at the research site. After Week 16, all subjects could add other approved and investigational antiretroviral agents to their study drugs following consultation and agreement between the sponsor and the principal investigator.

Participation in the protocol was limited to no more than 40 subjects with prior non-nucleoside reverse transcriptase (NNRTI) experience. Eligible subjects were stratified according to their viral burden at screen (≥ 500-40,000 copies/mL; >40,000 copies/mL). Data was also summarized by NNRTI experience. Subjects were to receive combination therapy with ABC, APV and EFV for a minimum of 48 weeks.

As expected, proportionally more subjects were asymptomatic at screening in the stratum with baseline viral load ≥500-40,000 copies/mL. Conversely, more subjects with a baseline viral load >40,000 copies/mL entered the study with a previous AIDS defining condition. Higher baseline CD4+ cell counts were observed among subjects

with baseline viral load ≤40,000 copies/mL. Finally, more subjects with advanced HIV disease at baseline (higher viral load, lower CD4+ cell counts and diagnosis of AIDS) were NNRTI experienced and conversely, NNRTI naïve subjects appeared to be less advanced in the progression of their HIV infection. The patient population for this study was heavily pretreated: 84% had received at least two PIs, 60% received at least three PIs, and 74% had received at least four NRTIs prior to study entry.

2.2. RCG Data Analysis Plan Issues

Prior antiretroviral therapy was available for regimens received within six months of study initiation. Therefore, a complete profile of prior ART exposure is not available. All subjects received three new therapies; therefore the new drug co-variate associated with the number of new drugs in the regimen was not included in any of the models. The second drug co-variate considered PI or NNRTI experience. Since all of the subjects were PI experienced, this drug co-variate focused on the NNRTI experience alone. There was a significant difference in the number of subjects with genotypic data (94) compared to the number of subjects with phenotypic data (64). Therefore caution needs to be exercised when comparing the results across populations.

2.3. Database Issues

This study was ongoing at the time of this report. The clinical database used for this report had not gone through a complete authorization process. Data beyond the week 24 window (> 224 days into the study) was not considered for this study with the exception of the next available PCR data in the case of a subject whose plasma viral load was not reaching levels below 400 copies/mL. Genotypic analysis of plasma samples was conducted using RT-PCR and ABI automated sequencing at Glaxo Wellcome. Phenotypic assays were conducted at Virco NV (Belgium).

3. RESULTS

The results presented in this report are similar to those reported in the 16-week clinical study report.

3.1. Study Population Accountability

In this study, 101 subjects were enrolled and 99 of them received study medication. Of the 99 treated subjects, 73 (74%) remained on the originally assigned study regimen with no deviations for at least 16 weeks. Of the 26 subjects with less than 16 weeks of original study medication, 24 discontinued due to an adverse event, and two discontinued for other reasons.

NRTI, NNRTI, and PI genotypic information is available for 94 of these subjects. Phenotypic data was available for 64 of the 99 subjects enrolled. Phenotype results for all three drugs in the regimen had to be present for a subject to be included in this analysis (n=64). In the dropouts as censored (DAC) analysis subset, eight of the 64 subjects were censored.

3.2. Prior Antiretroviral Therapy

The collection of prior antiretroviral therapy was limited to therapies received within six months of enrollment into the study. Therefore, we do not have a complete prior antiretroviral profile for these subjects. NNRTI experience was a stratification variable used upon enrollment into the study, complete information regarding this class of ART was available for these analyses. In the dropouts as failures (DAF) genotype population, all subjects were PI experienced, 40% were NNRTI experienced, and 98% were NRTI experienced (Table 1). The NNRTI stratification information was used to determine new drug co-variate associated with introduction of an NNRTI for subjects who were NNRTI naïve. Since everyone received three new drugs in their regimen, this new drug co-variate associated with number of new ARTs was not considered in any of the models. The prior ART summary was similar for the DAC genotype population as well as the DAF and DAC phenotype populations.

3.3. Baseline Immunology

All subjects in this study had detectable (> 400 copies/mL) virus at baseline. The baseline immunology of the DAC and DAF genotype and phenotype populations was similar. For the DAF genotype population, the median HIV-RNA PCR and CD4 count at baseline were 5.1 log 10 c/mL and 160 c/mm3 respectively (Table 1). For the DAF phenotype population, the median HIV-RNA PCR and CD4 count at baseline were 5.1 log 10 c/mL and 124 c/mm3 respectively (Table 2).

3.4. Baseline HIV-1 RNA Genotype

The genotype sensitivity score (GSS) and number of ART mutations were similar for the DAC and DAF analysis subsets. For both the DAF and the DAC analysis subsets, the median GSS was 2.0 with a range of 0 to 3. In the DAF analysis subset baseline, most subjects (88%) had at least three NRTI mutations present, 55% of the subjects had no NNRTI mutations present, and 82% of the subjects had at least four PI mutations present (Tables 4 and 5).

3.5. Baseline HIV-1 RNA Phenotype

The phenotype sensitivity score (PSS) and number of drugs in regimen with phenotypic sensitivities at 4 fold reduction (FR) cut-off and 10 FR cut-off were similar for the DAC and DAF analysis subsets. For both the DAF and the DAC analysis subsets, the median PSS at 4 FR cut-off and 10 FR cut-off was 2 and 3 respectively (Tables 6 and 7). In the DAF analysis subset, the 4 FR cut-off, the percents of subjects phenotypically sensitive to their NRTI (ABC), NNRTI (EFV), and PI (APV) regimen were 45%, 67%, and 58% respectively. For the 10 FR cut-off, the percents of subjects phenotypically sensitive to their NRTI (ABC), NNRTI (EFV), and PI (APV) regimen were approximately 94%, 73%, and 86% respectively.

3.6. Endpoint – Virologic Failure

The primary endpoint to be examined is the proportion of subjects with HIV-1 RNA PCR below 400 copies/mL at week 24. Virologic failure was assessed for the DAF and DAC analysis subsets using the algorithm provided in the RCG DAP (section 4.2.3.1). For the DAF genotype population, there were 23 successes, 71 failures, and no censored subjects. For the DAC genotype population, there were 23 successes, 53 failures, and 18 censored. In the DAF phenotype population, there were 16 successes, 48 failures, and none censored. In the DAC phenotype population, there were 16 successes, 40 failures, and eight censored.

3.7. Logistic Regression Models

The logistic regression analyses modeled the log odds of virologic failure. For positive parameter estimates, the log odds of failure increased as the value of the co-variate increased. For negative parameter estimates, the log odds of failure decreased as the value of the co-variate increased. The odds ratio gives an approximate risk for every unit increase in a co-variate. Unit increases were defined as follows:

- Baseline Viral Load – 1 log 10 HIV-1 RNA copies/mL increase
- GSS or PSS – 1 point increase
- Number of Genotype Mutations – 1 additional mutation
- NNRTI naïve (new drug co-variate) –naïve to experienced

The 95% confidence intervals (CI) for the odds ratios provide an estimate of the precision. The Hosmer and Lemeshow Goodness-of-Fit test provides a measure of how well the co-variates explain virologic failure. Small p-values correspond to models that do not fit well. The models with missing goodness-of-fit tests correspond to two-level co-variates with no degrees of freedom for the test statistic.

Tables 4 and 5 present the logistic models for the DAF and DAC genotype populations respectively. Models A, B, C, and D are univariate, and Models E, F, and G are multivariate. In the DAF analysis subset, Model F suggests that the genotype information is more predictive of virologic failure than baseline viral load. Most of the 95% confidence intervals were broad. The predictive value of the NNRTI naïve co-variate in Model B was not present in Models E or F. Similar results were seen in the DAC analysis subset (Table 5).

Tables 7 and 8 present the logistic models for the DAF and DAC phenotype populations respectively. In the DAF analysis subset, the 4 FR threshold did a better job in predicting virologic failure than the 10 FR threshold. The larger models, Models H, I, and J, did not fit well with the exception of Model G. The PSS at the 4 FR threshold exhibits the best association with virologic failure. Similar results were seen in the DAC analysis subset (Table 8) with the exception of a reduced fit in Model G and a better fit in Model H.

4. SUMMARY

We performed retrospective analyses of a dataset to explore the association between baseline resistance information (phenotype or genotype) with virologic failure (i.e., plasma HIV RNA from below the limit of detection via the Amplicor assay).

The dataset consisted of information from a Glaxo Wellcome sponsored clinical trial (CNAA2007). The patient population consisted of heavily pre-treated HIV-1 infected subjects with advanced HIV disease that received a combination ART containing ABC, APV and EFV. Subjects enrolled in the study were experiencing virologic failure (screening HIV-1 plasma RNA levels of ≥500 copies/mL) despite at least 20 weeks treatment with a treatment regimen containing at least one of the following PIs: indinavir, ritonavir, saquinavir and/or nelfinavir.

Logistic regression analyses showed that knowledge of the baseline genotype provided useful, explanatory information in the models. An increase in the number of baseline NRTI and NNRTI genotypic mutations was associated with virologic failure, and an increase in genotypic sensitivity was associated with a reduction in virologic failure.

Logistic regression analyses also showed that knowledge of the baseline phenotype provided useful, explanatory information in the models above and beyond the information provided by baseline viral load.

These analyses of this dataset provide some evidence that knowledge of baseline genotype and phenotype is associated with virologic outcome.

5. TABLES

Table 1
Summary of Prior Antiretroviral Therapy and Baseline Immunology
ABC+EFV+APV Treated Subjects from CNAA2007
With Genotype Data at Baseline

Characteristic	Statistic/Category	Analysis Subsets DAC/1	DAF/2
Baseline log10(PCR)	n	76	94
	Mean	4.935	4.941
	SD	0.674	0.671
	Median	4.986	5.058
	Min.	3.36	3.36
	Max.	6.60	6.60
Baseline PCR < 400 c/ml	n	76	94
	No	76 (100%)	94 (100%)
Baseline CD4 Count	n	76	94
	Mean	188.6	181.9
	SD	161.1	158.7
	Median	166.0	159.8
	Min.	10	10
	Max.	782	782
Prior Number of ARTs	n	76	94
	2	2 (3%)	3 (3%)
	3	22 (29%)	30 (32%)
	4	27 (36%)	29 (31%)
	5	19 (25%)	21 (22%)
	6	6 (8%)	10 (11%)
	7	0	1 (1%)
Prior NRTI Usage	n	76	94
	No	1 (1%)	2 (2%)
	Yes	75 (99%)	92 (98%)
Prior NNRTI Usage	n	76	94
	No	45 (59%)	56 (60%)
	Yes	31 (41%)	38 (40%)
Prior PI Usage	n	76	94
	Yes	76 (100%)	94 (100%)

/1 DAC - these patients are included in the dropouts as censored analysis strategy.
/2 DAF - these patients are included in the dropouts as failures analysis strategy.

Table 2
Summary of Prior Antiretroviral Therapy and Baseline Immunology
ABC+EFV+APV Treated Subjects from CNAA2007
With Phenotype Data at Baseline

Characteristic	Statistic/Category	Analysis Subsets DAC/1	DAF/2
Baseline log10(PCR)	n	56	64
	Mean	5.023	5.052
	SD	0.553	0.536
	Median	5.099	5.126
	Min.	3.99	3.99
	Max.	6.33	6.33
Baseline PCR < 400 c/ml	n	56	64
	No	56 (100%)	64 (100%)
Baseline CD4 Count	n	56	64
	Mean	167.5	162.2
	SD	148.1	146.2
	Median	129.0	124.0
	Min.	10	10
	Max.	607	607
Prior Number of ARTs	n	56	64
	2	2 (4%)	3 (5%)
	3	16 (29%)	19 (30%)
	4	21 (38%)	22 (34%)
	5	12 (21%)	13 (20%)
	6	5 (9%)	7 (11%)
Prior NRTI Usage	n	56	64
	No	1 (2%)	1 (2%)
	Yes	55 (98%)	63 (98%)
Prior NNRTI Usage	n	56	64
	No	31 (55%)	37 (58%)
	Yes	25 (45%)	27 (42%)
Prior PI Usage	n	56	64
	Yes	56 (100%)	64 (100%)

/1 DAC - these patients are included in the dropouts as censored analysis strategy.
/2 DAF - these patients are included in the dropouts as failures analysis strategy.

Table 3
Summary of Genotypic Sensitivity Scores and Number of Mutations
ABC+EFV+APV Treated from CNAA2007
With Genotype Data at Baseline

Characteristic	Statistic/Category	Analysis Subsets DAC/1	DAF/2
GSS for NRTIs in Regimen	n	76	94
	Mean	1.553	1.585
	SD	0.773	0.754
	Median	2.000	2.000
	Min.	0.00	0.00
	Max.	3.00	3.00
Number of NRTI Mutations	n	76	94
	0	2 (3%)	2 (2%)
	1	5 (7%)	7 (7%)
	2	2 (3%)	2 (2%)
	3	10 (13%)	13 (14%)
	4	15 (20%)	20 (21%)
	5	30 (39%)	35 (37%)
	6	8 (11%)	11 (12%)
	7	1 (1%)	1 (1%)
	8	2 (3%)	2 (2%)
	9	1 (1%)	1 (1%)
Number of NNRTI Mutations	n	76	94
	0	41 (54%)	52 (55%)
	1	20 (26%)	22 (23%)
	2	13 (17%)	15 (16%)
	3	2 (3%)	4 (4%)
	4	0	1 (1%)
Number of PI Mutations	n	76	94
	0	6 (8%)	9 (10%)
	1	1 (1%)	1 (1%)
	2	2 (3%)	2 (2%)
	3	3 (4%)	6 (6%)
	4	25 (33%)	28 (30%)
	5	20 (26%)	26 (28%)
	6	13 (17%)	13 (14%)
	7	5 (7%)	8 (9%)
	8	1 (1%)	1 (1%)

/1 DAC - these patients are included in the dropouts as censored analysis strategy.
/2 DAF - these patients are included in the dropouts as failures analysis strategy.

Table 4
Logistic Regression – Genotype – Drop-outs as Failures Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
94 Subjects with Genotype Data – Successes=23 and Failures=71

Model	Variable	Parameter Estimate	• ² p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
A	Baseline PCR	0.958	0.015	2.606	1.201	5.652	0.114
B	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	Missing
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	1.134	0.041	3.126	1.046	9.346	
C	Overall Genotype Score	-0.832	0.019	0.435	0.217	0.874	0.496
D	Number of NRTI Mutations	0.464	0.023	1.590	1.066	2.372	
	Number of NNRTI Mutations	2.073	0.004	7.950	1.937	32.628	0.804
	Number of PI Mutations	0.040	0.808	1.041	0.752	1.442	
E	Baseline PCR	0.661	0.129	1.936	0.825	4.540	
	Overall Genotype Score	-0.660	0.072	0.517	0.252	1.060	0.811
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.613	0.322	1.845	0.549	6.200	
F	Baseline PCR	0.408	0.398	1.503	0.587	3.850	
	Number of NRTI Mutations	0.465	0.028	1.592	1.053	2.407	0.905
	Number of NNRTI Mutations	2.255	0.008	9.531	1.807	50.277	
	Number of PI Mutations	0.029	0.865	1.030	0.735	1.443	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	-0.646	0.414	0.524	0.111	2.465	

Note: All subjects received three new antiretroviral therapies: ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the number of new antiretroviral therapies as a new drug co-variate in the models.

Table 5
Logistic Regression – Genotype – Drop-outs as Censored Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
76 Subjects with Genotype Data – Successes=23 and Failures=53

Model	Variable	Parameter Estimate	• ² p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
A	Baseline PCR	1.037	0.015	2.821	1.226	6.490	0.159
B	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	Missing
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	1.243	0.031	3.467	1.122	10.707	
C	Overall Genotype Score	-0.951	0.010	0.387	0.188	0.796	0.704
D	Number of NRTI Mutations	0.529	0.026	1.697	1.066	2.702	0.794
	Number of NNRTI Mutations	2.450	0.003	11.590	2.365	56.796	
	Number of PI Mutations	0.146	0.438	1.157	0.801	1.672	
E	Baseline PCR	0.713	0.127	2.040	0.816	5.098	
	Overall Genotype Score	-0.811	0.034	0.445	0.210	0.940	0.498
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.847	0.178	2.333	0.681	7.995	
F	Baseline PCR	0.525	0.319	1.690	0.602	4.745	
	Number of NRTI Mutations	0.496	0.037	1.642	1.030	2.616	0.958
	Number of NNRTI Mutations	2.435	0.006	11.421	2.007	64.986	
	Number of PI Mutations	0.170	0.390	1.185	0.804	1.746	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	-0.225	0.787	0.799	0.156	4.093	

Note: All subjects received three new antiretroviral therapies: ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the number of new antiretroviral therapies as a new drug co-variate in the models. As per RCG DAP, there were 18 subjects who were censored from these analyses.

Table 6
Summary of Phenotypic Sensitivity Scores and Number of Resistances
ABC+EFV+APV Treated Subjects from CNAA2007
With Phenotype Data at Baseline

Characteristic	Statistic/Category	Analysis Subsets DAC/1	DAF/2
Pheno Score (<= 4 FR)	n	56	64
	Mean	1.7	1.7
	SD	0.9	0.9
	Median	2.0	2.0
	Min.	0	0
	Max.	3	3
Number of Phenotypic Siesitivities <= 4 Fold Reduction for Drugs in the Study Regimen			
Number of NRTI	n	56	64
	> 4	30 (54%)	35 (55%)
	<= 4	26 (46%)	29 (45%)
Number of NNRTI	n	56	64
	> 4	19 (34%)	21 (33%)
	<= 4	37 (66%)	43 (67%)
Number of PI	n	56	64
	> 4	25 (45%)	27 (42%)
	<= 4	31 (55%)	37 (58%)
Pheno Score (<= 10 FR)	n	56	64
	Mean	2.5	2.5
	SD	0.6	0.6
	Median	3.0	3.0
	Min.	0	0
	Max.	3	3
Number of Phenotypic Sensitivities <= 10 Fold Reduction for Drugs in the Study Regimen			
Number of NRTI	n	56	64
	> 10	2 (4%)	4 (6%)
	<= 10	54 (96%)	60 (94%)
Number of NNRTI	n	56	64
	> 10	16 (29%)	17 (27%)
	<= 10	40 (71%)	47 (73%)
Number of PI	n	56	64
	> 10	8 (14%)	9 (14%)
	<= 10	48 (86%)	55 (86%)

/1 DAC - these patients are included in the dropouts as censored analysis strategy.
/2 DAF - these patients are included in the dropouts as failures analysis strategy.

Table 7
Logistic Regression – Phenotype – Drop-outs as Failures Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
64 Subjects with Phenotype Data – Successes=16 and Failures=48

Model	Variable	Parameter Estimate	• ² p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
A	Baseline PCR	1.263	0.037	3.535	1.078	11.586	0.296
B	New Drug Co-Variates 1) Number of New ARTs 2) PI or NNRTI Naïve with PI or NNRTI in Regimen	NA 0.621	NA 0.310	NA 1.862	NA 0.561	NA 6.180	Missing
C	Overall Phenotype Score using a 4 FR cut-off	-1.188	0.003	0.305	0.138	0.676	0.735
D	Overall Phenotype Score using a 10 FR cut-off	-0.997	0.104	0.369	0.111	1.229	Missing
E	4 FR cut-off # of NRTI Pheno Sensitivities # of NNRTI Pheno Sensitivities # of PI Pheno Sensitivities	 -1.605 -0.518 -0.510	 0.017 0.073 0.448	 0.201 0.219 0.601	 0.053 0.042 0.161	 0.754 1.149 2.239	0.856
F	10 FR cut-off # of NRTI Pheno Sensitivities # of NNRTI Pheno Sensitivities # of PI Pheno Sensitivities	 -12.559 -2.013 0.385	 0.977 0.063 0.640	 0.000 0.134 1.469	 0.000 0.016 0.293	 999 1.117 7.360	0.991
G	Baseline PCR Overall Phenotype Score using a 4 FR cut-off New Drug Co-Variates 1) Number of New ARTs 2) PI or NNRTI Naïve with PI or NNRTI in Regimen	1.557 -1.270 NA 0.345	0.035 0.004 NA 0.624	4.746 0.281 NA 1.412	1.113 0.119 NA 0.356	20.233 0.666 NA 5.596	0.788

Note: All subjects received three new antiretroviral therapies: ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the number of new antiretroviral therapies as a new drug co-variate in the models.

Table 7
Logistic Regression – Phenotype – Drop-outs as Failures Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
64 Subjects with Phenotype Data – Successes=16 and Failures=48

Model	Variable	Parameter Estimate	• [2] p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
H	Baseline PCR	1.271	0.045	3.565	1.029	12.345	0.275
	Overall Phenotype Score using a 10 FR cut-off	-0.999	0.144	0.368	0.097	1.404	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.185	0.786	1.203	0.318	4.556	
I	4 FR cut-off						
	Baseline PCR	1.623	0.031	5.066	1.157	22.175	0.127
	# of NRTI Pheno Sensitivities	-1.846	0.011	0.158	0.038	0.657	
	# of NNRTI Pheno Sensitivities	-1.523	0.122	0.218	0.032	1.500	
	# of PI Pheno Sensitivities	-0.530	0.474	0.589	0.138	2.510	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.116	0.886	1.123	0.230	5.499	
J	10 FR cut-off						
	Baseline PCR	1.397	0.035	4.405	1.106	14.796	0.153
	# of NRTI Pheno Sensitivities	-12.182	0.977	0.000	0.000	999	
	# of NNRTI Pheno Sensitivities	-2.405	0.046	0.090	0.009	0.957	
	# of PI Pheno Sensitivities	0.561	0.538	1.752	0.293	10.462	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	-0.380	0.614	0.684	0.156	2.989	

Note: All subjects received three new antiretroviral therapies ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the new drug co-variates in the models.

Table 8
Logistic Regression – Phenotype – Drop-outs as Censored Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
56 Subjects with Phenotype Data – Successes=16 and Failures=40

Model	Variable	Parameter Estimate	• ² p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
A	Baseline PCR	1.109	0.066	3.030	0.930	9.872	0.432
B	New Drug Co-Variates 1) Number of New ARTs 2) PI or NNRTI Naïve with PI or NNRTI in Regimen	NA 0.789	NA 0.207	NA 2.200	NA 0.646	NA 7.492	Missing
C	Overall Phenotype Score using a 4 FR cut-off	-1.439	0.002	0.237	0.097	0.583	0.890
D	Overall Phenotype Score using a 10 FR cut-off	-0.981	0.113	0.375	0.112	1.260	Missing
E	4 FR cut-off # of NRTI Pheno Sensitivities # of NNRTI Pheno Sensitivities # of PI Pheno Sensitivities	 -1.709 -1.849 -0.880	 0.016 0.036 0.209	 0.181 0.157 0.411	 0.045 0.028 0.103	 0.724 0.883 1.643	0.966
F	10 FR cut-off # of NRTI Pheno Sensitivities # of NNRTI Pheno Sensitivities # of PI Pheno Sensitivities	 -12.306 -2.131 0.480	 0.983 0.050 0.579	 0.000 0.119 1.616	 0.000 0.014 0.296	 999 1.003 8.815	0.937
G	Baseline PCR Overall Phenotype Score using a 4 FR cut-off New Drug Co-Variates 1) Number of New ARTs 2) PI or NNRTI Naïve with PI or NNRTI in Regimen	1.491 -1.548 NA 0.679	0.062 0.002 NA 0.362	4.441 0.213 NA 1.973	0.927 0.080 NA 0.457	21.283 0.562 NA 8.505	0.349

Note: All subjects received three new antiretroviral therapies: ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the number of new antiretroviral therapies as a new drug co-variate in the models. As per RCG DAP, eight subjects were censored from these analyses.

Table 8
Logistic Regression – Phenotype – Drop-outs as Censored Outcome
ABC/EFV/APV Treated Subjects from CNAA2007
56 Subjects with Phenotype Data – Successes=16 and Failures=40

Model	Variable	Parameter Estimate	• ² p-value	Odds Ratio	95% CI Low	95% CI High	Hosmer & Lemeshow Goodness-of-Fit Test
H	Baseline PCR	1.113	0.080	3.045	0.875	10.593	
	Overall Phenotype Score using a 10 FR cut-off	-0.968	0.157	0.380	0.099	1.450	0.815
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.401	0.557	1.494	0.391	5.705	
I	4 FR cut-off						
	Baseline PCR	1.588	0.053	4.893	0.979	24.465	0.288
	# of NRTI Pheno Sensitivities	-2.091	0.008	0.124	0.026	0.581	
	# of NNRTI Pheno Sensitivities	-1.624	0.107	0.197	0.027	1.421	
	# of PI Pheno Sensitivities	-0.973	0.220	0.378	0.080	1.788	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	0.566	0.518	1.761	0.317	9.733	
J	10 FR cut-off						
	Baseline PCR	1.323	0.047	3.755	1.018	13.847	0.083
	# of NRTI Pheno Sensitivities	-12.234	0.982	0.000	0.000	999	
	# of NNRTI Pheno Sensitivities	-2.403	0.045	0.090	0.009	0.949	
	# of PI Pheno Sensitivities	0.690	0.479	1.994	0.295	13.496	
	New Drug Co-Variates						
	1) Number of New ARTs	NA	NA	NA	NA	NA	
	2) PI or NNRTI Naïve with PI or NNRTI in Regimen	-0.125	0.868	0.882	0.201	3.871	

Note: All subjects received three new antiretroviral therapies: ABC (NRTI), EFV (NNRTI), and APV (PI). There was no need to include the number of new antiretroviral therapies as a new drug co-variate in the models. As per RCG DAP, eight subjects were censored from these analyses.