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Antiretroviral Medication Adherence and Class-Specific Resistance in a Large Prospective Clinical Trial

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Abstract

Objective—To assess the association between adherence to antiretroviral therapy and the presence of class-specific antiretroviral medication resistance.

Design—Secondary analysis of prospective clinical trial data

Methods—Participants randomized to the protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) strategies of the Community Programs for Clinical Research on AIDS (CPCRA) Flexible Initial Retrovirus Suppressive Therapies (FIRST) Study were included. Adherence was measured by 7-day self-report. Virological failure was defined as an HIV-RNA > 1000 at or after 4 months. The association between cumulative adherence and the development of class-specific genotypic resistance was assessed by Cox regression analysis.

Results—Included were 457 and 446 antiretroviral naïve participants on the PI and NNRTI strategies respectively. The median time to initial virological failure in the PI strategy was 1.2 years;

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135 (30%) individuals failed with resistance. The median time to initial virological failure in the NNRTI strategy was 3.0 years; 127 (28%) failed with resistance. No association was found between cumulative adherence and PI resistance (HR 1.1, 95% CI 0.9 – 1.4 per 10% lower adherence). However, lower cumulative adherence was associated with an increased risk of NNRTI resistance at initial virological failure (HR 1.2, 95% CI 1.1 – 1.3 per 10% lower adherence). In both strategies lower cumulative adherence was associated with an increased risk of nucleoside reverse transcriptase inhibitor (NRTI) resistance at initial virological failure.

Conclusions—Adherence-resistance relationships are class-specific. For NRTIs and NNRTIs, initial virological failure with resistance is more likely at lower levels of cumulative adherence.

Keywords

adherence; antiretroviral therapy; HIV; virological failure; antiretroviral resistance

Introduction

Antiretroviral resistance and inadequate antiretroviral medication adherence are the most important predictors of virological failure during treatment for human immunodeficiency virus (HIV) infection [1–5]. These two factors are linked in that inadequate antiretroviral medication adherence is a major predictor of the development of antiretroviral medication resistance during HIV treatment [6]. Antiretroviral medication adherence-resistance relationships are class-specific and, in some classes, medication-specific [7]. Knowledge of the association between adherence and resistance may be useful in determining optimal treatment combinations and optimal ways to sequence antiretroviral regimens to improve long-term clinical outcomes.

Current analyses of class-specific antiretroviral medication adherence-resistance relationships are lacking long-term prospective follow-up and have generally included small numbers of treated individuals. This analysis was conducted to assess the relationship between antiretroviral medication adherence and the development of class-specific antiretroviral medication resistance in previously antiretroviral naïve participants enrolled in the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) Flexible Initial Retrovirus Suppressive Therapies (FIRST, CPCRA 058) Study [8].

Methods

Participants

The CPCRA was a National Institutes of Health-sponsored clinical trials group that conducted community based HIV/AIDS research targeting underserved populations. The CPCRA FIRST Study was a randomized clinical trial assessing different initial treatment strategies for antiretroviral naïve HIV-infected adults [8]. From 1999 through 2002 participants were randomly allocated (1:1:1) to one of three initial strategies: the protease inhibitor (PI) strategy (PI[s] + nucleoside reverse transcriptase inhibitors [NRTIs]); the non-nucleoside reverse transcriptase inhibitor (NNRTI) strategy (an NNRTI + NRTIs); or the 3-class strategy (PI[s] + an NNRTI + NRTI[s]). Clinicians could choose individual medications within the assigned strategy or those medications were randomly assigned for participants enrolled in class-specific substudies (14% of participants) [9]. This analysis was limited to the PI and NNRTI strategies in order to evaluate initial regimens that are similar to those currently recommended. One major difference is that nelfinavir was the most common protease inhibitor in FIRST, and nelfinavir is not a currently recommended PI for initial therapy [10]. Written informed consent was obtained from all participants in order to enroll in the FIRST Study [8].

Data Collection and Definitions

Participant demographics were obtained at study entry. At baseline, months 1 and 4, and then every 4 months thereafter data obtained included the following: antiretroviral regimen, CD4 lymphocyte count, HIV-1 RNA level, and self-reported antiretroviral medication adherence (except at baseline). Genotypic antiretroviral resistance testing was done at the time of initial virological failure, defined as an HIV-1 RNA level > 1000 copies/ml at or after four months of follow-up. Resistance was determined using the TRUGENE HIV-1 Genotyping Kit (Bayer HealthCare AG) and CPCRA interpretive algorithm v4.0. The algorithm presented drug susceptibilities for the seven NRTI, three NNRTI, and six PI antiretroviral medications approved for use during FIRST.

Adherence was assessed using the CPCRA Adherence Self-Report Form, a global 7-day recall asking participants to estimate their level of adherence to each individual antiretroviral medication in their regimen [11]. For each medication prescribed, a value was assigned based on whether the participant indicated taking all (100%), most (80%), about half (50%), some (20%), or none (0%) of their pills during the previous 7 days. Antiretroviral adherence was calculated at each visit as the average for all components of the regimen. Fixed dose combination formulations were included in adherence calculations once. An individual not on antiretroviral therapy was assigned an adherence value of zero for that visit. An adherence report form was considered missing if a protocol required visit was missed or if a visit was attended but the adherence form was not submitted. Missing forms were not assigned an adherence value. For each participant, we calculated cumulative adherence at each visit as the average of all adherence values up to and including that visit.

Statistical Analysis

This study is a post-hoc analysis of prospectively collected clinical trial data. All participants who were randomized to the PI or NNRTI strategies of FIRST who had at least one adherence measurement and for whom study-defined virological failure could be determined (i.e., had at least one HIV RNA measurement at or after the 4-month visit) were included in the analyses. CD4 cell counts and HIV RNA measurements were recorded at the screening and randomization visits; the average of the values at these two visits was considered to be the baseline measurement. Characteristics of the randomized strategy groups were compared using generalized linear models or the chi-square test.

Separately for the randomized NNRTI and PI strategies, Cox proportional hazards regression models were used to evaluate the impact of cumulative adherence on time to virological failure with the presence of class-specific antiretroviral medication resistance. The analyses were intention to treat, with participants included in their randomized strategy even if there was a strategy switch prior to initial virological failure. Two models were created; both were adjusted for baseline characteristics (age, gender, race/ethnicity, and baseline CD4 cell count and HIV RNA levels) and had a time-updated variable for cumulative adherence. The first model evaluated cumulative adherence as a continuous-valued variable. The second model evaluated cumulative adherence as a categorical variable (0–79%, 80–99%, and 100%). The second model was included because the published literature suggested a non-linear association between adherence and resistance for some medication-classes [7]. In both models, individuals without virological failure during follow-up were assumed not to have antiretroviral medication resistance. These analyses demonstrate the association between adherence and resistance in a population initiating antiretroviral therapy.

Because participants and clinicians were free to change from an initial strategy to an alternative at any time during follow-up, sensitivity analyses with censoring at first switch from randomized strategy if it occurred prior to initial virological failure were performed. In

addition, Cox regression models were repeated for non-randomized subgroups within the PI strategy: participants who initiated antiretroviral therapy with a ritonavir boosted PI versus a nonboosted PI.

Final analyses were undertaken to describe antiretroviral medication resistance in the subpopulation of participants experiencing virological failure. These calculations exclude individuals not experiencing virological failure during follow-up. In these analyses, participants who experienced virological failure and had no strategy switch prior to initial failure were classified according to their cumulative adherence at the time of initial failure (0–79%, 80–99%, and 100%). The proportion of individuals with class-specific resistance in each adherence category was assessed. These analyses demonstrate the association between adherence and resistance in a population failing antiretroviral therapy.

Statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute, Inc., Cary, North Carolina, USA). Hazard ratios are given with 95% confidence intervals (CI). All *p* values presented are two-sided.

Results

In FIRST, 933 participants were randomized to the PI (*n* = 470) or NNRTI (*n* = 463) strategies. Thirty participants (3%) were excluded from these analyses (13 in the PI strategy; 17 in the NNRTI strategy) due to no adherence measurement, no HIV RNA measurement at or after the 4-month visit, or no resistance test results available at initial virological failure. There were no significant differences in baseline characteristics between included participants randomized to the PI versus NNRTI strategies (data not shown). Detailed characteristics of the FIRST population have been published previously [8]. In brief, the population averaged 38 years of age, were racially diverse (54% Black, 26% White, 17% Latino/a, and 3% other), and 22% were female. The antiretroviral naive population assessed in these analyses had advanced HIV disease with a mean CD4 lymphocyte count of 212 cells/ul and 39% had a prior AIDS diagnosis.

Specific antiretroviral medications used in FIRST have been previously reported [8]. In summary, in the PI strategy the most common PIs used were nelfinavir (61%), indinavir/ritonavir (13%), indinavir (11%), and lopinavir/ritonavir (8%). In the NNRTI strategy the most common NNRTIs used were efavirenz (63%) and nevirapine (37%). In both strategies the most common NRTI combinations used were zidovudine/lamivudine (56%), stavudine/lamivudine (20%), abacavir/lamivudine (9%), and didanosine/stavudine (9%).

Among participants in the PI strategy, 326 (71%) of 457 developed initial virological failure a median of 1.2 years after initiating therapy (Table 1). At the time of virological failure, antiretroviral medication resistance within at least one class was present in 135 (30%); 37 (8%) had PI resistance and 121 (26%) had NRTI resistance. Among participants in the NNRTI strategy, 262 (59%) of 446 developed virological failure a median of 3.0 years after initiating therapy. Antiretroviral medication resistance was present in 127 (28%); 112 (25%) had NNRTI resistance and 63 (14%) had NRTI resistance. Two- or three-class antiretroviral medication resistance at initial virological failure developed in 39 (9%) participants randomized to PI and 50 (11%) participants randomized to NNRTI. The most common resistance mutations were for PIs the D30N (*n* = 26), for NNRTIs the K103N (*n* = 81), and for NRTIs the M184I/V (*n* = 171). A comprehensive list of specific resistance mutations in FIRST has been reported [12].

Cumulative self-reported adherence at the time of initial virological failure or censoring was excellent in both the PI (median 91.6%, interquartile range [IQR] 77.1 – 100%) and NNRTI (median 93.3%, IQR 76.4 – 100%) strategies (*p* = 0.96). Within the PI strategy, median cumulative adherence levels at the time of initial virological failure were 89.8% (IQR 66.7 – 100) and 93.1% (IQR 79.1 – 100) for the boosted and nonboosted PI recipients respectively.

When assessing cumulative adherence prior to initial virological failure or censoring as a categorical variable in the PI strategy, 148 participants had 100% cumulative adherence, 187 had 80–99% adherence, and 120 had 0–79% adherence. In the NNRTI strategy 120 participants had 100% cumulative adherence, 204 had 80–99% adherence, and 125 had 0–79% adherence.

The results of multivariate Cox regression analyses of time to initial virological failure with class-specific antiretroviral medication resistance are presented in Table 2. In the PI strategy no association was found between cumulative adherence (continuous variable) and PI resistance at initial virological failure (HR 1.1, 95% CI 0.9–1.4, per 10% lower cumulative adherence). In the NNRTI strategy, lower cumulative adherence increased the risk of NNRTI resistance at initial virological failure (HR 1.2, 95% CI 1.1–1.3 per 10% lower cumulative adherence). In both strategies lower cumulative adherence was associated with an increased risk of NRTI resistance (Table 2). The results from on-treatment analyses, with censoring at first switch from randomized strategy, were similar in direction, magnitude, and significance (data not shown).

Results from multivariate Cox proportional hazards regression analyses assessing cumulative adherence as a time-updated categorical value (0–79%, 80–99%, and 100%) are presented in Figure 1. In the PI strategy, once again, there was no association between cumulative adherence and PI resistance, while in the NNRTI strategy there was an increased risk of NNRTI resistance in the 80–99% (HR 2.3, 95% CI 1.4–3.7) and the 0–79% (HR 6.5, 95% CI 3.9–10.7) cumulative adherence groups compared to individuals with 100% cumulative adherence. In both strategies there was an increased risk of NRTI resistance in individuals with cumulative adherence levels less than 100% (Figure 1). The greatest risk of NNRTI resistance was in individuals with the lowest adherence (0–79%).

Among participants randomized to the PI strategy, 116 (25%) were prescribed a ritonavir boosted PI at study entry, 338 (74%) were prescribed a nonboosted PI, and 3 (1%) did not initiate therapy with a PI (Table 3). Of those on a boosted PI regimen 52% were on indinavir/ritonavir, 31% were on lopinavir/ritonavir, and 10% were on saquinavir/ritonavir. Nonboosted versus boosted PI use was associated with a significantly higher risk of PI resistance (10% compared to 2%; $p<0.01$) and NRTI resistance (29% compared to 19%; $p=0.03$) at initial virological failure. In multivariate Cox regression analysis there was no relationship between cumulative adherence and PI resistance for participants initiating therapy with a nonboosted PI. Similar analyses were not possible for those who initiated with a boosted-PI due to the rarity of events in this group. The two individuals failing boosted PI based therapy with PI resistance were no longer receiving boosted PI based therapy at the time of initial virological failure.

In a final analysis, participants experiencing virological failure prior to strategy switch were categorized by their cumulative adherence at initial virological failure: 0–79%, 80–99%, and 100%. Within each cumulative adherence category the proportion of participants with class-specific antiretroviral medication resistance at the time of virological failure are presented in Figure 2. The percentage of individuals failing nonboosted PI based therapy with PI resistance (5–30%, depending on cumulative adherence category, Figure 2a) was lower than the percentage of individuals failing NNRTI based therapy with NNRTI resistance (37–75%). The percentage of individuals with NRTI resistance at the time of virological failure was higher in participants failing nonboosted PI based therapy (38–64%) compared to participants failing NNRTI based therapy (7–39%) or boosted PI based therapy (0–41%). At the time of virological failure, NRTI resistance was highest among participants with 80–99% cumulative adherence on all three classes of therapy (Figure 2b).

Discussion

The data presented here represent one of the largest studies with the longest duration of follow-up to assess class-specific adherence-resistance relationships in antiretroviral naïve individuals initiating antiretroviral therapy. In analyses including all individuals, no association between cumulative adherence and PI resistance was found. For NNRTIs and NRTIs we found a significant association between lower levels of cumulative adherence and resistance at initial virological failure. In analyses that included only individuals failing antiretroviral therapy, higher levels of cumulative adherence were associated with the presence of nonboosted PI, NNRTI, and NRTI resistance mutations. The development of PI resistance mutations in individuals initiating boosted PI based therapy was rare. Finally, NRTI resistance was more common in individuals receiving nonboosted PI based therapy compared to NNRTI or boosted PI based therapy.

In this study there was no apparent association between cumulative adherence to PI based antiretroviral therapy and failure with PI resistance. For ritonavir boosted PI based therapy the reason was clear – the development of PI resistance was extremely rare at all adherence levels. The fact that PI resistance is rare in individuals failing boosted PI based therapy has been shown previously [13,14]. For nonboosted PIs others have shown that the highest risk of PI resistance occurs at moderate to high levels of adherence [15,16]. We did not find a similar association. The lack of association between PI adherence and resistance in this study may have to do with the adherence assessment tool. Self-reported adherence tends to overestimate true adherence [17], making it more difficult to identify associations between adherence and outcomes at higher levels of adherence. The lack of association may also be due to the short duration of follow-up prior to initial virological failure in this sub-population (median time to failure 1.1 years). It takes longer for resistance to develop when more mutations are required for full resistance (the genetic barrier to resistance), as seen with many PIs [7].

For NNRTIs, at lower levels of cumulative adherence, the risk of NNRTI resistance at initial virological failure was increased. In the subset of individuals with virological failure however, resistance was common at all adherence levels. Prior studies showed similar findings [18,19]. Thus, in a population of individuals initiating NNRTI based antiretroviral therapy the highest risk of failing with resistance occurs at the lowest levels of adherence. This finding is largely due to the potency of NNRTIs; where potency is defined as the likelihood that a given antiretroviral regimen will suppress HIV-1 viremia below the limits of standard assay detection [7]. On a potent regimen, most individuals with moderate to excellent adherence have complete viral suppression and therefore are unlikely to develop resistance. However, in a population of individuals failing antiretroviral therapy the risk of NNRTI resistance is high at all adherence levels. Two factors are responsible for this relationship. First, most NNRTIs have a low genetic barrier to resistance making the development of resistance during viral replication common. Second, NNRTI resistant virus typically retains its ability to replicate in the presence or absence of drug (fitness and replicative capacity [7]), allowing resistant virus to out-compete wild-type virus at most drug exposure levels [18].

NRTI resistance, like NNRTI resistance, was more common at lower levels of cumulative adherence. However, in individuals failing virologically, NRTI resistance was seen at high but not perfect levels of cumulative adherence, similar to other studies [16,20]. Of note, 88% of NRTI mutations led to lamivudine and emtricitabine resistance via the M184I/V mutation. Thus, these results more closely approximate the adherence-resistance relationship for deoxycytidine analogs, rather than the whole NRTI class. The deoxycytidine analog NRTI adherence resistance relationship is defined by the fitness cost of the M184I/V mutation (making resistance at low levels of adherence less likely) and the low genetic barrier to

resistance that makes resistance common in the setting of viral replication at higher adherence levels [7].

The potency of antiretroviral regimens is the largest single determinant of the development of antiretroviral resistance for all antiretroviral classes. The more potent the regimen, the less likely is viral replication (at all levels of adherence) and the less likely is the development of antiretroviral resistance [19]. While the fitness cost of resistance and the genetic barrier to resistance are important, they matter most during active viral replication (i.e., during virological failure) [7]. The message to HIV-infected individuals should be clear – complete virological suppression remains the goal of antiretroviral therapy. The best way to achieve complete virological suppression is to optimize adherence to all components of multi-drug antiretroviral therapy [21]. It is true that there is a theoretical concern of increasing the risk of development of antiretroviral resistance in patients with active viral replication while on therapy. However, the increased chance of successful virological suppression with improved adherence appears to outweigh the risk involved as shown in our analyses.

Another important finding in this analysis is that NRTI resistance is more prevalent in individuals failing nonboosted PI based therapy than in those failing NNRTI or boosted PI based therapy. A previous comparison of nonboosted versus boosted PI based therapy showed similar findings [20]. This finding now extends to NNRTIs, which showed similar rates of development of NRTI resistance compared to boosted PIs in all adherence categories. Together, these data suggest that it is the potency of the concomitant drugs, rather than their genetic barrier to resistance or fitness cost of resistance that is most important in determining the incidence of resistance to concomitant drugs. Again these analyses support that any efforts at improving adherence will have the greatest likelihood of decreasing the development of resistance overall.

Most participants who failed antiretroviral therapy in the FIRST Study did not have antiretroviral resistance mutations. Resistance within any antiretroviral medication class at initial virological failure occurred in less than 30% of randomized participants and in less than 50% of participants with virological failure in the PI and NNRTI strategies of the FIRST Study. One possible explanation for this finding is that patients may have completely interrupted therapy, acknowledged or not acknowledged. Also, resistance mutations arise as random mutations that occur over time and are dependent on the level, not just the presence, of viral replication. Thus individuals with low level viremia or intermittent viremia may not develop resistance for longer periods of time. Other possibilities to explain the lack of resistance in most individuals failing therapy include low frequency mutations not picked up by population sequencing or non-sequenced resistance mutations like connection domain or RNase H mutations in reverse transcriptase or GAG mutations that affect protease inhibitor susceptibility [22–24].

There are several important limitations to this study. First, we did not have baseline resistance data. However, baseline resistance was carried out on a random sample of 491 (35%) FIRST participants, with rates of any resistance at about 10% [25]. Lack of baseline resistance could have impacted our results if resistance within an individual class of medications had a differential impact on response rates to regimens containing that class. Second, due to the timing of the study, there were relatively few ritonavir boosted PI based regimens, and the receipt of boosted versus nonboosted PI was not randomized. Third, in the Cox regression analyses the time to virological failure varied greatly between individuals and different adherence patterns likely occurred. The impact of the timing of nonadherence (early, late, and continuous) has not been well described and could have potentially affected these analyses. Finally, our analyses utilized self-reported adherence as this was the only adherence measure used in the FIRST Study; supporting data such as serum antiretroviral medication levels were

not available. Self-reported adherence likely overestimates true adherence and may make it difficult to discern adherence-resistance relationships at higher levels of adherence.

Conclusion

This study is one of the largest prospective analyses of class-specific adherence-resistance relationships to date. These analyses support that in a population initiating antiretroviral therapy the higher the level of cumulative adherence the better the outcomes. Excellent adherence and full virological suppression remain the goal of antiretroviral therapy. These analyses also demonstrate why boosted-PI and NNRTI based antiretroviral therapies have become preferred over nonboosted PI based options. Not only are rates of failure higher for nonboosted PI based therapy, so are rates of resistance development for the nonboosted PI and the accompanying NRTIs. As we learn more about adherence-resistance relationships this data can likely be applied to emerging classes of therapy [7]. This knowledge can help provide the foundation for rational design of medication combinations and regimen sequencing to improve the longevity of currently available therapies in the era of HIV as a chronic illness [26].

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Figure 1.

Risk (hazard ratio) of initial virological failure with resistance by randomized strategy and cumulative adherence categories in the CPCRA FIRST Study.

*hazard ratios with 95% confidence intervals, compared to individuals with 100% cumulative adherence

Figure 2.

Class-specific resistance at initial virological failure by cumulative adherence category in the CPCRA FIRST Study, assessed in individuals experiencing virological failure during follow-up on NNRTIs (n = 136), Nonboosted PI (n = 164), and Ritonavir Boosted PI (n = 41). Panel A denotes NNRTI or PI resistance. Panel B denotes NRTI resistance.

Table 1

Antiretroviral medication resistance at initial virological failure by randomized strategy in the CPCRA FIRST Study

	NNRTI STRATEGY (N = 446)		PI STRATEGY (N=457)	p-VALUE
Virological failure, N (%)	262 (59%)		326 (71%)	<0.01
Median time to virological failure or censoring (years)	3.0		1.2	<0.01

Medication resistance at virological failure, N (%)				
	Entire Population (n = 446)	Individuals Failing (n = 262)	Entire Population (n = 457)	Individuals Failing (n = 326)
Any Class	127 (28%)	127 (48%)	135 (30%)	135 (41%)
NNRTI	112 (25%)	112 (43%)	18 (4%)	18 (6%)
PI	5 (1%)	5 (2%)	37 (8%)	37 (11%)
NRTI	63 (14%)	63 (24%)	121 (26%)	121 (37%)
Cytidine Analogs	55 (12%)	55 (21%)	116 (25%)	116 (36%)
None	319 (72 %)	135 (52%)	322 (70%)	190 (58%)
1 Class	77 (17%)	77 (29%)	96 (21%)	96 (29%)
2 or 3 Class	50 (11%)	50 (19%)	39 (9%)	39 (12%)

Table 2

Hazard ratios (95% CI) from multivariate Cox regression analyses of time to initial virological failure* with antiretroviral resistance in the CPCRA FIRST Study, adherence is presented as a continuous variable

Variables	NNRTI STRATEGY		PI STRATEGY	
	NNRTI Resistance	NRTI Resistance	PI Resistance	NRTI Resistance
Age (Per 10 year increase)	0.71 (0.57 – 0.89)	0.79 (0.59 – 1.06)	0.91 (0.62 – 1.34)	0.79 (0.64 – 0.97)
Female	1.29 (0.84 – 1.98)	1.24 (0.69 – 2.23)	0.96 (0.44 – 2.07)	0.87 (0.55 – 1.37)
Latino Ethnicity [†]	1.44 (0.71 – 2.90)	1.21 (0.48 – 3.01)	1.52 (0.45 – 5.15)	0.73 (0.39 – 1.37)
Black Race [†]	3.10 (1.79 – 5.36)	2.65 (1.33 – 5.28)	3.69 (1.36 – 10.02)	2.02 (1.27 – 3.21)
Prior AIDS	0.89 (0.59 – 1.36)	1.31 (0.75 – 2.30)	0.87 (0.43 – 1.76)	0.74 (0.50 – 1.11)
Baseline CD4 Count (Per 100 cell/ul increase)	0.90 (0.78 – 1.04)	0.82 (0.66 – 1.01)	0.62 (0.45 – 0.85)	0.71 (0.61 – 0.82)
Baseline HIV-RNA (Per log ₁₀ copies/ml increase)	1.81 (1.33 – 2.46)	1.51 (1.01 – 2.28)	1.56 (0.91 – 2.68)	1.37 (1.05 – 1.80)
Cumulative Adherence (Per 10% decrease) ^{#‡}	1.24 (1.14 – 1.34)	1.19 (1.06 – 1.34)	1.09 (0.88 – 1.36)	1.28 (1.18 – 1.38)
No. of Participants	446	446	457	457
No. of Events	112	63	37	121

* Time to HIV-RNA level > 1000 copies/mL at or after month 4

[†] Reference group is white and other

[#] Time-updated variable

[‡] Adjusted for not being on antiretroviral therapy

Table 3

Antiretroviral medication resistance at initial virological failure by PI type (non-randomized comparison) in the CPCRA FIRST Study

	<u>BOOSTED PI (N=116)</u>	<u>NONBOOSTED PI (N=338)</u>	<u>P-VALUE</u>
Virological failure, N (%)	83 (72%)	241 (71%)	0.96
Median time to virological failure or censoring (years)	1.5	1.1	0.73
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Medication resistance at virological failure, N (%)			
Any Class	27 (23%)	108 (32%)	0.08
NNRTI	11 (9%)	7 (2%)	<0.01
PI	2 (2%)	35 (10%)	<0.01
NRTI	22 (19%)	99 (29%)	0.03
None	89 (77 %)	230 (68%)	0.19
1 Class	20 (17%)	76 (22%)	
2 or 3 Class	7 (6%)	32 (9%)	