

## **CPCRA 058 (FIRST) Executive Summary**

**3 February 2006**

### INTRODUCTION

Long-term comparative data on the effectiveness of different antiretroviral treatment (ART) regimens with which to initiate therapy are lacking. In 1998 and 1999 three large trials were initiated to evaluate the effect of beginning ART with one of the following combinations: 1) nucleoside reverse-transcriptase inhibitors (NRTIs) + protease inhibitor treatment (PI); NRTIs + non-nucleoside reverse transcriptase inhibitors (NNRTIs); and NRTI(s) + PI + NNRTI treatment. Each of the trials involved two different 2-class regimens and one 3-class regimen. The Flexible Initial Retrovirus Suppressive Therapies (FIRST) study, described here, allowed investigators and participants to choose drugs to be used within each class, by specifying prior to randomization drugs to be taken initially for all of the strategy arms. The other 2 studies (ACTG 384, INITIO) specified the individual drugs in each starting regimen. FIRST is the largest of the three trials and has the longest follow-up.

### METHODS

#### Study Design

FIRST was carried out by the Community Programs for Clinical Research on AIDS (CPCRA) by 18 clinical trial units that coordinated the work of 80 clinical research sites in the United States. Eligible persons were randomly allocated to one of three starting regimens on a background of NRTI treatment: 1) PI; 2) NNRTI; or 3) PI + NNRTI. Randomization was stratified by clinical unit and CD4+ cell count ( $\leq 200$  versus  $> 200$  cells/mm<sup>3</sup>) (36 strata total);

schedules were generated using randomly mixed permuted blocks of size 3 and 6. Assignments were obtained by calling a toll free number at the statistical center for CPCRA.

Prior to randomization, participants and investigators could either pre-select the specific drugs used in each class or consent to an additional randomization of drugs within each class: 1) indinavir, nelfinavir, or 2 PIs of choice (boosted PIs were considered as 2 PIs) for the PI class; 2) nevirapine (NVP) or efavirenz (EFV) for the NNRTI class; and 3) abacavir (ABC) + lamivudine (3TC) or didanosine (ddI) + stavudine (d4T) for the NRTI class. For the two 2-class strategies, two NRTIs were to be used; for the 3-class strategy, one NRTI or two NRTIs could be used.

The findings of the NRTI randomized substudy have been reported already (MacArthur RD, Chen L, Peng G, et al; HIV Clinical Trials 2004;5:361-70). The results of the PI and NNRTI nested substudies are included in this report as appendices. All treatments were administered in an open-label manner. With the exception of ABC and 3TC, which were donated by GlaxoSmithKline, and ddI and d4T, donated by Bristol-Myers Squibb, and were made available to some participants through a central drug distribution facility, all other drugs were prescribed by the participant's physician.

Guidelines prepared by the U.S. Department of Health and Human Services were to be followed for changing ART for drug failure. To the extent possible, when drugs were discontinued for toxicity, drugs within the same class were to be substituted in order to maintain persons on their randomly assigned treatment strategy.

The FIRST trial had two major objectives: 1) to compare the PI and NNRTI strategies; and 2) to compare the 3-class strategy with the pooled results of the two 2-class strategies. An important secondary objective was to compare the 3 strategies with one another. Major endpoints were a composite of AIDS or death or a follow-up CD4+ count < 200 (the latter

component was considered only among persons with a baseline CD4+ count of 200 cells or greater) (primary endpoint for NNRTI versus PI comparison); difference in CD4+ cell count after 32 months of follow-up (primary endpoint for 3-class versus 2-class comparison). Thirty-two months was deemed ample to compare the immunologic effects of the different strategies. Secondary endpoints considered in this report include death, AIDS or death, time to change of the initial treatment strategy, virologic control, and grade 4 adverse events.

### Study Subjects

HIV-infected persons were eligible if they were 13 years of age or older, had not previously used a PI or NNRTI, had not used NRTI(s) for cumulative time of > 4 weeks, and had not used 3TC for > 1 week. Women of childbearing potential were required to use a barrier method of birth control to be eligible for the study.

### Data Collection

The protocol was approved by the local institutional review board of each site. Written informed consent was obtained from each participant.

CD4+ cell counts were locally determined at a screening visit and at the time of randomization (average is considered baseline); plasma for HIV RNA levels was obtained at the same time points and centrally determined using the Roche Ultrasensitive assay with a lower limit of detection of 50 copies/mL. Following randomization, participants were seen at month 1, month 4, and every 4 months thereafter. At each visit, CD4+ cell count, HIV RNA level, non-fasting blood lipids, glucose, AST, and ALT were measured, the participant's clinical status was

assessed, changes in ART for  $\geq 30$  days were documented, and self-reported adherence was assessed. Self-reported adherence was based on ART drugs prescribed in the 7 days prior to the follow-up visit.

Genotypic resistance testing was performed at four possible time points: baseline, first virologic failure, month 12, and month 36. At baseline, genotypic resistance tests were performed on a random sample of 504 persons enrolled in the FIRST study, and the results have been reported previously (Novak RM, Chen L, MacArthur RD, et al; CID 2005;40:468-74). The definition of virologic failure evolved during the course of the study. At the start of the study in 1999, virologic failure was defined as a confirmed viral load measurement greater than 2000 copies/ml, with the confirmation viral load obtained within 60 days of the first measurement. Genotypic resistance tests were performed on the same plasma specimen that was used for the confirmation viral load test. In January 2002 the study objectives (and the definition of virologic failure) were modified, so that genotypic resistance tests would be performed the first time a follow-up viral load measurement was greater than 1000 copies/ml (no confirmation necessary). For patients who already had genotypic resistance testing performed due to a viral load greater than 2000 copies/ml, an additional genotypic resistance test was performed on a stored sample if there was an earlier viral load measurement between 1000 and 2000 copies/ml. At the 12- and 36-month visits, genotypic resistance tests were performed for all persons with a viral load measurement greater than 1000 copies/ml at that visit.

Resistance was defined as definite resistance by genotype, using the TRUGENE HIV-1 Genotyping Kit and OpenGene DNA Sequencing System, Bayer Diagnostics (Version 4.0), which presents drug susceptibilities for 16 drugs (7 NRTI, 3 NNRTI, and 6 PI). Testing for atazanavir and tipranavir was not available. The presence of specific drug-resistance mutations

was determined, using the October 2004 International AIDS Society-USA (IAS-USA) tables. Those tables include 54 possible allelic mutations (22 NRTI mutations, 15 NNRTI mutations, and 17 major PI mutations) at 36 different codons.

Disease progression events were defined as the occurrence of an AIDS-defining clinical event according to modified CDC criteria. Events considered to be evidence of disease progression were reviewed by a clinical events committee blinded to treatment group. Those events meeting confirmed or probable criteria were considered endpoints.

Grade 4 (severe or life-threatening events) adverse events, including laboratory abnormalities, clinical signs and symptoms, diseases other than AIDS-defining events, and clinical syndromes, were reported irrespective of the presumed relationship to ART and coded using a toxicity manual developed by the Division of AIDS and based on modified ICD-9 criteria.

### Sample Size and Data Monitoring

For the first primary objective comparing the two 2-class strategies, NNRTI + NRTIs versus PI + NRTIs, the primary endpoint was progression to AIDS or death or a CD4+ cell count decline to less than 200 cells among persons who entered with a CD4+ count greater than or equal to 200 cells/mm<sup>3</sup>. For this comparison, 292 primary events were planned assuming that there would be no treatment difference in the first 3 months of follow-up and a hazard ratio (HR) (NNRTI versus PI strategy) of 0.67 after 3 months for an overall median follow-up of 5.3 years. Power was 0.80 and the significance level was set at 0.05 (2-sided). Depending on the event rate assumed and duration of follow-up, sample size estimates ranged from 420 to 570 persons per group to obtain the required number of events.

For the comparison of the two 2-class strategy groups (pooled) with the 3-class strategy group, the primary outcome was the difference in CD4+ cell count after 32 months between the two groups. Total sample size, assuming a 2:1 allocation (2-class versus 3-class) was 1,176 persons to detect a 40 cell difference between groups assuming the standard deviation of change in CD4+ from baseline was 220 cells/mm<sup>3</sup>.

During the study all investigators were blinded to accruing results. An independent Data and Safety Monitoring Board (DSMB) reviewed interim analyses at least once per year. At the last meeting of the DSMB of FIRST in November 2004, the DSMB recommended closure of FIRST in the 3<sup>rd</sup> quarter of 2005. The DSMB noted that the required follow-up information for the comparison of the 3- versus 2-class strategies had been achieved (all participants had been followed for at least 32 months), and recognized that the required number of events for the comparison of the two 2-class strategies (292) might not be achieved (248 events occurred through the closing date). Nevertheless, they felt that results for all of the study arms should be unblinded together.

As a guideline, during the trial, the DSMB used O'Brien-Fleming boundaries and the Lan-DeMets spending function at interim analyses. The FIRST study was reviewed 6 times by the DSMB.

### Statistical Analyses

All analyses were by intention to treat – participants were counted in the strategy groups to which they were originally randomized for all analyses. Analyses of the primary endpoint of the NNRTI versus PI comparison, composite of AIDS or death or a follow-up CD4+ count < 200 (the latter component was considered only among persons with a baseline CD4+ count of 200

cells or greater), were stratified by clinical unit and baseline CD4+ cell count (consistent with the randomization). Other analyses were not stratified because, for many analyses, the strata were too sparse. For the primary endpoint for the 2- versus 3-class comparison, difference in CD4+ cell count after 32 months of follow-up, covariates corresponding to clinical unit and baseline CD4+ were included.

Time to event methods, e.g., Kaplan-Meier survival curves and Cox's proportional hazards model, were used to compare treatment groups for survival, progression to AIDS or death, progression to AIDS or death or CD4+ decline to < 200 cells, grade 4 events, and time to a change in treatment strategy. The censoring date used in clinical event analyses was the closing date (September 16, 2005) or the date the participant became lost to follow-up for the event considered. For analyses that considered CD4+ cell count as part of the composite, follow-up was censored on the date of the last recorded CD4+ cell count measurement. Time to event analyses are summarized with two hazard ratios (NNRTI versus PI and 3-class versus 2-class) and with 95% confidence intervals. In addition, p-values corresponding to a 2 degree of freedom omnibus test for comparing the 3 randomized groups are cited.

Stratified analysis of variance (18 strata corresponding to clinical units) was used to compare the 2- and 3-class strategy groups for change in CD4+ cell count from baseline. All CD4+ cell count levels at or after 32 months were used and baseline CD4+ cell count was used as a covariate. Longitudinal regression models were also used to compare change in CD4+ cell counts during follow-up. In addition, slopes are cited (increase in count per month). Longitudinal models for binary data were used to compare the treatment groups for the percent with HIV RNA level < 50 copies/mL at each follow-up. These analyses were supplemented with

time to event analyses that examine time to HIV RNA < 50 copies/mL and time to loss of virologic control (defined as HIV RNA > 50 copies/mL at or after 8-month visit ) or death.

For time to virologic failure associated with drug resistance, the three treatment strategies were compared with Kaplan-Meier cumulative event curves, log-rank tests and proportional hazards regression models. The censoring date used for first virologic failure associated with drug resistance was the date of the last recorded viral load measurement (for those with no virologic failure) or the date the plasma sample was obtained (for those with virologic failure). For sensitivity analyses, selected on-treatment analyses also were performed. Differences in proportions of persons were analyzed using chi-squared tests. Descriptive summaries of resistance patterns present at first virologic failure are presented, although they are not protected by randomization.

Major outcomes are summarized for pre-defined baseline subgroups: age, race, gender, history of injecting drug use, co-infection with hepatitis, and levels of CD4+ cell count and viral load prior to initiating treatment. In addition to these subgroups, the information collected prior to randomization on the specific ART drugs to be used for each strategy are used to define subgroups. These subgroups are investigated to assess whether different ART drugs used for each strategy (e.g., NRTI drugs used for the 2- and 3-class strategies) influence the treatment difference. Lack of homogeneity of treatment differences for subgroups was assessed by including treatment by subgroup interaction terms in Cox models and regression models. P-values corresponding to these tests of homogeneity are cited for each subgroup.

Statistical analyses were performed using SAS (Version 8.2). All p-values cited are 2-sided.

## RESULTS

Between February 1999 and January 2002, 1,397 persons were randomized: 470 to the PI + NRTI group; 463 to the NNRTI +NRTI group; and 464 to the PI + NNRTI + NRTI group. (Figure 1). One site with 30 participants closed during the study on February 22, 2004, for administrative reasons. Follow-up of participants at that site were censored on the closing date.

The treatment groups were well balanced in terms of demographic and other baseline characteristics (Table 1). Overall, the median age was 38 years; 20.6% of persons were female; and over 70% were non-white -- 53.8% black and 17.0% Latino. Median HIV RNA level and CD4+ cell count were 143,844 copies/mL and 163 cells/mm<sup>3</sup>, respectively. Nearly 38% of participants reported a history of a prior AIDS event. The great majority of persons had a clinical history and/or CD4+ cell count for which current U.S. guidelines indicate ART should be initiated. Sixty-two percent reported an AIDS clinical event or a CD4+ cell count less than or equal to 200 cells/mm<sup>3</sup>; 18.3% had a CD4+ between 201 and 350 cells/mm<sup>3</sup>; and 19.7% had a CD4+ greater than 350 cells/mm<sup>3</sup>. Approximately 6% of participants were co-infected with hepatitis B (hepatitis B surface antigen positive) and 19.6% were co-infected with hepatitis C (hepatitis C IgG positive).

Nelfinavir (NFV) was the most frequently used PI among persons assigned to the PI + NRTI group (60%) followed by a ritonavir (RTV)-boosted PI (25.5%) (Table 2). Among persons assigned the NNRTI + NRTI strategy, efavirenz (EFV) was prescribed for 62% of persons; nevirapine (NVP) was prescribed for 36% of persons. Similar nucleoside combinations were used for persons in the PI and NNRTI strategies. For the 3-class strategy, NFV (62%) and EFV (51%) were also the most commonly used PI and NNRTI; however, NVP was used more

often in the 3-class arm (45%) than in the 2-class arm (36%). For all 3 treatment groups, the most common NRTI combinations were zidovudine (AZT) + lamivudine (3TC) and stavudine (d4T) + 3TC. These combinations were used more often for the 2-class strategies than the 3-class strategy. In addition, a single NRTI, usually d4T, was used by 24% of persons assigned the 3-class strategy.

### Follow-up and Adherence to Assigned Strategy

Median follow-up was 60 months and extended to 79 months for some participants. In the year prior to closeout, the percent of surviving persons with a CD4+ cell count determined was 88% for each of the 3 strategies. The percent of surviving persons with at least one CD4+ cell count determined after 32 months (the primary outcome for the 2- versus 3-class strategy) was 93.1% for the PI strategy, 91.7% for the NNRTI strategy, and 92.7% for the 3-class strategy (Figure 1).

Approximately 97% of participants initiated their randomly assigned strategy (Table 3). Approximately 68% of persons on the PI + NRTI arm changed strategy (stopped all PIs or switched to another strategy by adding an NNRTI); 58% of persons on the NNRTI + NRTI arm changed strategy (stopped all NNRTIs or switched to another strategy by adding a PI); and 80% of persons assigned the 3-class strategy discontinued the PI or NNRTI. The fraction of follow-up time on the assigned strategy was greatest for the NNRTI strategy (70% of follow-up) and shortest for the 3-class strategy (46%). Approximately 14% of follow-up in all 3 groups was spent not taking ART.

The greater fraction of follow-up time on the assigned strategy for the NNRTI arm than the PI and 3-class arms resulted in exposure to fewer ART drugs for the NNRTI arm. Among

persons assigned the NNRTI strategy, 45% only received 3 different ART drugs during follow-up, 20% received 4 or 5 ART drugs, 16% received 6 or 7 ART drugs, and 19% received 8 or more different ART drugs. By comparison, for those assigned the PI strategy, these percentages were 20%, 29%, 24%, and 27%, and for the 3-class strategy, these percentages were 3%, 42%, 27%, and 28%, respectively. Approximately 32% of persons assigned the NNRTI strategy were subsequently prescribed a PI whereas 43% of persons assigned the PI strategy were subsequently prescribed an NNRTI. Of those participants initially prescribed nelfinavir, 37% subsequently received a double PI.

Self-reported adherence for persons prescribed ART was assessed at each follow-up visit and was very high. At most visits more than two-thirds of persons in each treatment group reported 100% adherence to their ART treatments. There was no difference in self-reported adherence among the three treatment groups ( $p=0.36$ ).

Toxicity was identified as the reason for changing strategy by 29% of persons assigned the 3-class strategy, 17% assigned the PI strategy, and by 13% assigned the NNRTI strategy.

#### HIV RNA Levels During Follow-up

Time-to-event analysis indicated that the time to HIV RNA < 50 copies/mL varied significantly among treatment groups (Figure 2;  $p<0.001$ ). Persons assigned the NNRTI strategy and the 3-class strategy were more likely to achieve an HIV RNA level below 50. Longitudinal regression analysis indicated that the NNRTI and 3-class strategies were also more likely to result in levels < 50 copies/mL throughout follow-up than the PI strategy (Figure 3;  $p<0.001$  for both comparisons).

Hazard ratios and 95% confidence intervals (CIs) for achievement of an HIV RNA level < 50 copies/mL were 1.43 (95% CI 1.24-1.65) for the NNRTI versus PI strategy; and 1.13 (95% CI: 1.00- 1.28) for 3-class versus 2-class strategy. Hazard ratios for time to a HIV RNA level > 50 copies/mL at or after the 8-month visit or death were 0.63 (95% CI 0.55-0.73) for the NNRTI versus PI strategy; and 1.08 (95% CI: 0.95- 1.22) for 3-class versus 2-class strategy. For time to virologic failure (HIV RNA level > 1000 copies/mL after 4-month visit), hazard ratios were 0.66 (95% CI 0.56 - 0.77) for the NNRTI versus PI strategy; and 0.87 (95% CI 0.75 - 1.0) for the 3-class versus 2-class strategy.

#### CD4+ Cell Count During Follow-up

On average, CD4+ cell count increased rapidly in all 3 treatment groups. Median increases after 8 months of follow-up were 116, 125, and 123 cells/mm<sup>3</sup> for the PI, NNRTI, and 3-class strategies, respectively. Corresponding increases after 24 months of follow-up were 197, 202, and 183. Based on a longitudinal regression analysis that utilized all follow-up CD4+ cell counts, there was no evidence of a difference among the 3 treatment groups (Figure 4; p=0.77). Similarly, the rate of change of CD4+ cell count after 8 months of follow-up was similar for the 3 treatment groups (1.7 cells/month for the PI arm, 1.6 for the NNRTI arm, and 1.5 cells/month for the 3-class strategy arm; p=0.92).

Average changes in CD4+ cell count at or after 32 months of follow-up were 227 and 234 cells/mm<sup>3</sup> for the 2- and 3-class strategies, respectively (p=0.62; 95% CI: -20 to 33). A sensitivity analysis in which deaths were assigned a worst rank score did not alter this finding (p=0.72).

## Clinical Endpoint Summary

Overall, 188 persons died and 302 persons experienced a disease progression event or died (Table 4 and Figure 5). Neither of these outcomes differed significantly among the 3 randomized groups. In all three groups the rate of events was greatest in the first 6 months of the study (13.2 per 100 person years versus 3.9 afterwards). Pooled cumulative rates for disease progression or death after 6, 12, 24, 36, and 48 months of follow-up were 6%, 9%, 13%, 17%, and 20% (Figure 5). The most commonly occurring opportunistic events were esophageal candidiasis (53 persons), *Pneumocystis jirovecii* pneumonia (35 persons), *Mycobacterium avium* complex infection (25 persons), lymphoma (22 persons), cryptococcosis (21 persons), and cytomegalovirus infection (20 persons).

Grade 4 adverse events were more common than disease progression events – overall, 439 persons experienced at least one event. The rate of grade 4 events also did not vary by treatment group ( $p=0.98$ ). Elevations of liver function tests were the most common grade 4 events and they occurred more often on those taking an NNRTI-containing regimen. Rates of elevations of liver function tests per 100 person years were 0.7, 1.4 and 1.5 for persons assigned the PI, NNRTI and 3-class strategy ( $p=0.03$ ). Other common grade 4 events for PI, NNRTI and 3-class strategies were: anemia (rates per 100 person years = 0.7, 1.0, and 0.8;  $p=0.65$ ); neutropenia (0.8, 0.7 and 0.8 per 100 person years;  $p=0.98$ ); and gastrointestinal (GI) symptoms (nausea, diarrhea, vomiting and other GI complaints) (1.0, 1.1, and 1.1 per 100 person years;  $p=0.93$ ).

Of the 302 persons who died or experienced disease progression, 95 persons were in the PI arm, 98 were in the NNRTI arm and 109 were in the 3-class strategy arm. Hazard ratios and

95% CIs for the 3-class versus 2-class strategy and for the NNRTI versus PI strategy were 1.14 (95% CI: 0.91-1.45) and 1.07 (0.80-1.41), respectively.

For the composite outcome of disease progression (AIDS or death) or a CD4+ decline to < 200 cells/mm<sup>3</sup> (the latter only considered for persons with a baseline CD4+ count of 200 cells/mm<sup>3</sup> or greater), there was not a significant difference between the NNRTI and PI strategy (HR=1.02; 95% CI: 0.79-1.31).

### Subgroup Findings

Table 5 compares the 2 and 3-class strategies for selected subgroups defined by baseline characteristics, including whether a single or 2 NRTIs were pre-specified for the 3-class arm. Treatment differences were similar across a range of subgroups.

Table 6 compares the PI and NNRTI strategies for selected baseline subgroups. For comparison with two other trials that used specific drugs, subgroups according to whether AZT+3TC and nelfinavir and efavirenz were pre-specified were examined. Among persons for whom AZT+3TC was pre-specified, 98% were prescribed the combination. Similarly, 99.2% of persons assigned to the PI strategy for whom nelfinavir was pre-specified and 98.8% of persons assigned to the NNRTI strategy for who efavirenz was pre-specified, were prescribed the indicated drug. A significant treatment-subgroup interaction (p=0.02) was found for the groups defined according to whether NFV and EFV were pre-specified to be used prior to randomization. For those pre-specifying NFV and EFV the risk of progression was greater on the NNRTI strategy arm than the PI strategy arm (HR=1.55); the opposite was true for those who did not pre-specify NFV or EFV (HR=0.81).

## Resistance

Of 1360 persons with a viral load measurement after 4 months of follow-up, 866 (63.7%) experienced virologic failure. Of those who experienced virologic failure, genotypic test results were available for 856 persons (98.8%) and were either not performed or did not have usable results for 10 persons (1.2%). Time to virologic failure associated with drug resistance in any class was marginally different for the NNRTI versus PI strategies (hazard ratio 0.78, 95% CI 0.62-1.0; Table 7). Time to virologic failure associated with NRTI resistance was significantly different for all treatment strategies. The hazard ratios and 95% CIs were 0.43 (0.31 – 0.58) for the NNRTI versus PI strategy; 0.27 (0.19 – 0.39) for the PI+NNRTI versus PI strategy; and 0.65 (0.43 – 0.96) for the PI+NNRTI versus NNRTI strategy. Multi-class resistance was present in 9%, 11%, and 6% of those in the PI, NNRTI, and PI+NNRTI strategies; the difference was significant between the NNRTI and PI+NNRTI strategies ( $p=0.005$ ).

Of the 856 persons with genotypic resistance test results at first virologic failure, 326 (38%) were in the PI strategy, 262 (31%) were in the NNRTI strategy, and 268 (31%) were in the PI+NNRTI strategy. Table 8 shows the frequency of mutations found in persons with genotypic resistance test results at first virologic failure. In the protease gene, the most common mutations found were D30N (in 41% of those with a protease mutation), L33I/F (in 24%), and L90M (in 24%). In the reverse transcriptase gene, the most common NNRTI mutations were K103N (in 61% of those with a NNRTI mutation), Y181C/I (in 24%) and G190A/S (in 16%); the most common NRTI mutation was M184I/V (in 79% of those with a NRTI mutation).

In the PI strategy, 58.6% of those with resistance test results at first virologic failure had no resistance (53.4% were sensitive to all drugs in the panel), 29.4% had single-class resistance (25.2% had resistance to only NRTIs), and 12.0% had multi-class resistance (Table 9). In the

NNRTI strategy 51.1% had no resistance (44.3% were sensitive to all drugs), 29.4% had single-class resistance (24.4% had resistance to only NNRTIs), and 19.5% had multi-class resistance. In the PI+NNRTI strategy, 52.6% had no resistance (47.8% were sensitive to all drugs), 37.3% had single-class resistance (30.2% were resistant to only NNRTIs), and 10.1% had multi-class resistance.

At first virologic failure in the PI, NNRTI, and PI+NNRTI strategies, 67%, 58%, and 45% respectively were on their randomized treatment strategy; while 24%, 32%, and 32% were not on any antiretroviral drugs (Table 10). Of those who were not on ART, the median time off therapy prior to virologic failure was 83, 89, and 80 days for the PI, NNRTI, and PI+NNRTI strategies, respectively. Of those with resistance test results at first virologic failure in the PI strategy arm, drug resistance was present in 50.6% of those on antiretroviral therapy at the time of failure, 12.7% of those not on antiretroviral therapy, and 41.4% overall (Table 11). In the NNRTI strategy arm, drug resistance was present in 60.7% of those on antiretroviral therapy, 23.8% of those not on antiretroviral therapy, and 48.9% overall. In the PI+NNRTI strategy arm, the corresponding percents were 57.9%, 24.7%, and 47.4%, respectively.

For those with genotypic resistance test results at first virologic failure, cross-resistance within a class is described in Table 12. Resistance to only lamivudine in the NRTI class was found in 91.7%, 71.4%, and 82.1% of those with NRTI resistance in the PI, NNRTI, and PI+NNRTI strategy arms, respectively. Resistance to only nelfinavir in the PI class was found in 62.2%, 40.0%, and 36.4% of those with PI resistance in the PI, NNRTI, and PI + NNRTI strategy arms, respectively.

## SUMMARY

CPCRA 058 (FIRST) is a large, long-term, randomized trial comparing three different antiretroviral strategies for initial therapy in antiretroviral-naïve HIV-infected persons. The protocol opened in February 1999, and randomized 1397 persons over 3 years to one of three strategies: 1) PI+NRTIs, 2) NNRTI+NRTIs, or 3) PI+NNRTI+NRTI(s). The two primary objectives of the study were: 1) to compare the PI+NRTIs and NNRTI+NRTIs strategies; and 2) to compare the 3-class strategy with the pooled results of the two 2-class strategies. The protocol closed in September 2005 with a median followup of 5 years. Major findings include:

- 1) A 3-class regimen was not superior to a 2-class regimen for virologic, immunologic or clinical outcomes. Adherence to the 3-class strategy was less than to either of the 2-class strategies. Persons assigned to the 3-class strategy discontinued therapy due to toxicity more than those assigned to the 2-class strategies.
- 2) Initial treatment with an NNRTI-based regimen and a PI-based regimen resulted in similar rates of AIDS events or death or decline in CD4+ cell count < 200.
- 3) An NNRTI-based regimen was superior to a PI-based regimen for rate of virologic suppression to <50 copies/mL and persistence of suppression over follow-up. Thus, this difference should be taken into consideration in interpreting the virologic results of the 2-class versus 3-class comparison.
- 4) Time to virologic failure associated with resistance to any drug was shortest in the PI-based strategy. Multi-class resistance developed more frequently in the NNRTI-based strategy.

**Table 1****Baseline Characteristics by Treatment Group**

<b>Characteristic</b>	<b>PI + NRTIs (N = 470)</b>	<b>NNRTI + NRTIs (N = 463)</b>	<b>2-Class Strategies (N = 933)</b>	<b>PI + NNRTI + NRTIs (3-Class Strategy) (N = 464)</b>	<b>Total (N = 1,397)</b>
Age (years) (Median, IQR)	38 (31 – 44)	38 (32 – 43)	38 (32 – 44)	38 (31 – 44)	38 (32 – 44)
Female (%)	22.8	20.7	21.8	18.3	20.6
Race/Ethnicity					
Black (%)	54.3	53.8	54.0	53.2	53.8
Latino (%)	17.7	16.6	17.1	16.8	17.0
White (%)	24.3	27.4	25.8	27.4	26.3
Other (%)	3.8	2.2	3.0	2.6	2.9
Intravenous drug use (%)	15.3	15.2	15.3	14.7	15.1
Hepatitis B (%)	5.7	5.9	5.8	7.1	6.2
Hepatitis C (%)	21.5	19.7	20.6	17.5	19.6
Prior AIDS (%)	39.1	38.7	38.9	35.3	37.7
No Prior AIDS and:					
CD4+ ≤ 200	23.4	23.8	23.6	25.6	24.3
CD4+ 201 – 350	18.7	18.4	18.5	17.9	18.3
CD4+ > 350 and HIV RNA < 100,000	12.3	13.4	12.9	17.2	14.3
CD4+ > 350 and HIV RNA ≥ 100,000	6.4	5.8	6.1	3.9	5.4
Baseline <sup>+</sup> CD4+ (cells/mm <sup>3</sup> ) (Median, IQR)	162.8 (44.5 – 329.0)	169.5 (36.0 – 329.0)	164.5 (39.0 – 329.0)	149.3 (31.8 – 337.0)	162.5 (36.0 – 331.5)
Baseline <sup>+</sup> HIV-RNA (copies/mL) (Median, IQR)	148,195 (38,700-424,297)	148,947 (34,017-430,935)	148,947 (37,110-428,330)	126,361 (41,402-349,540)	143,844 (38,418-400,147)

+ Average of screening and baseline levels.

**Table 2****Antiretroviral Treatment (ART) Prescribed Following Randomization**

<b>Initial ART</b>	<b>PI + NRTIs (N = 470)</b>		<b>NNRTI + NRTIs (N = 463)</b>		<b>2-Class Strategies (N = 933)</b>		<b>PI + NNRTI + NRTIs (3-Class Strategy) (N = 464)</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>PI</b>								
NFV	282	60.0	5	1.1	287	30.8	288	62.1
IDV	52	11.1	0	0	52	5.6	51	11.0
RTV Boosted PI	120	25.5	0	0	120	12.9	104	22.4
Other 2PIs	3	0.6	0	0	3	0.3	4	0.9
Single PI	4	0.9	0	0	4	0.4	7	1.5
<b>NNRTI</b>								
EFV	0	0	289	62.4	289	31.0	236	50.9
NVP	3	0.6	165	35.6	168	18.0	208	44.8
Other	0	0	1	0.2	1	0.1	10	2.2
<b>NRTI</b>								
AZT + 3TC	258	54.9	264	57.0	522	55.9	205	44.2
d4T + ddI	43	9.1	39	8.4	82	8.8	38	8.2
ABC + 3TC	41	8.7	39	8.4	80	8.6	41	8.8
d4T + ABC	18	3.8	12	2.6	30	3.2	4	0.9
d4T + 3TC	98	20.9	93	20.1	191	20.5	49	10.6
Other 2NRTIs	5	1.1	8	1.7	13	1.4	5	1.1
Single NRTI	2	0.4	1	0.2	3	0.3	110	23.7
3NRTIs	1	0.2	2	0.4	3	0.3	2	0.4
No ART started within 30 days of randomization	4	0.9	3	0.6	7	0.8	6	1.3

**Table 3****Adherence to Treatment Strategies During Follow-up**

	<b>PI + NRTIs</b> <b>(N = 470)</b>	<b>NNRTI + NRTIs</b> <b>(N = 463)</b>	<b>2-Class Strategies</b> <b>(N = 933)</b>	<b>PI + NNRTI + NRTIs (3-Class Strategy) (N = 464)</b>
Initiated Randomized Strategy (%)	97.4	97.0	97.2	96.3
Changed Strategy at Least Once (%)	67.9	57.7	62.8	79.5
Percent of Follow-up Time				
On Strategy	63.6	70.0		46.0
On Alternate Strategy	15.3	13.0		35.5
Other	2.8	0.9		--
On NRTI only	4.7	2.7		3.7
No AR	13.5	13.5		13.8
At Least One Treatment Change (%)	86.6	71.5	79.1	87.7
ART Exposure (Median Months, IQR)				
PI	35.1 (16.6 – 52.8)	0 (0 – 11.6)		38.6 (13.6 – 54.6)
NNRTI	0 (0 – 16.8)	41.0 (17.1 – 57.5)		29.5 (10.8 – 53.9)
NRTIs	49.9 (35.9 – 62.4)	51.9 (35.1 – 62.0)		50.5 (32.3 – 61.1)

**Table 4**  
**Major Endpoints by Treatment Group**

	Number of Events and Rate per 100 Person Year								Hazard Ratio (95% CI)		P-value For Difference Among 3 Randomized Group (2 df)
	PI + NRTIs (N = 470)		NNRTI + NRTIs (N = 463)		2-Class Strategies (N = 933)		PI + NNRTI + NRTIs (3-Class Strategy) (N = 464)		NNRTI vs. PI	3-Class vs. 2-Class	
	N	Rate	N	Rate	N	Rate	N	Rate			
Death	60	2.8	56	2.6	116	2.7	72	3.5	0.95 (0.66 – 1.37)	1.28 (0.95 – 1.71)	0.26
AIDS or Death	95	4.8	98	5.1	193	5.0	109	5.7	1.07 (0.80 – 1.41)	1.14 (0.91 – 1.45)	0.49
AIDS or Death Or CD4+ < 200	126	6.7	122	6.7	248	6.7	140	7.8	1.02 (0.79 – 1.31)	1.15 (0.94 – 1.42)	0.41
Grade 4 Events	147	8.7	147	8.9	294	8.8	145	8.9	1.02 (0.81 – 1.28)	1.01 (0.83 – 1.23)	0.98
AIDS or Grade 4 Event or Death	187	11.6	191	12.4	378	12.0	192	12.5	1.06 (0.87 – 1.30)	1.04 (0.88 – 1.24)	0.76

**Table 5**

**CD4 (Average Change from Baseline) of Month 32+  
by Selected Baseline Subgroups**

Baseline Subgroup	2-Class Strategies		3-Class Strategy		3-Class vs. 2-Class			Interaction P-Value
	N	Mean Change	N	Mean Change	Diff	S.E.	P-Value	
CD4+ (cells/mm <sup>3</sup> )								0.25
<= 200	438	258.4	214	281.1	20.74	17.0	0.24	
> 200	365	189.3	179	176.6	-10.5	21.6	0.63	
HIV-RNA (copies/mL)								0.97
< 100,000	339	182.8	177	188.2	8.39	20.6	0.68	
100,000 +	464	259.3	216	270.6	7.42	17.8	0.68	
POD CD4 composite								0.46
Prior AIDS	303	252.1	125	289.1	28.75	22.5	0.20	
NO POD CD4 <= 200	190	247.1	101	256.2	1.79	25.1	0.94	
CD4 > 200	310	190.1	166	177.7	-10.2	22.7	0.65	
Age								0.11
< 40 years	467	207.1	237	234.4	24.56	17.8	0.17	
40 + years	336	254.6	156	232.1	-18.9	20.6	0.36	
Gender								0.56
Male	628	220.7	323	232.3	11.51	14.3	0.42	
Female	175	249.5	70	238.9	-7.76	35.8	0.83	
Race								0.83
Latino	136	259.7	66	283.5	20.04	31.8	0.51	
Black	426	201.4	208	199.1	-0.31	18.4	0.99	
White/Other	241	253.8	119	265.9	11.33	24.4	0.64	
IV Drug Use								0.79
No	691	237.6	340	241.4	4.64	14.7	0.75	
Yes	111	163.0	53	182.9	15.54	32.1	0.63	
Hepatitis B								0.30
-	712	228.4	342	230.4	2.94	14.4	0.84	
+	44	196.8	27	255.1	59.72	49.3	0.23	
Hepatitis C								0.60
-	641	237.9	328	246.5	8.35	15.2	0.58	
+	159	179.9	64	166.0	-9.61	28.4	0.77	
Pre-spec NRTI in 3-class								0.52
1 NRTI	122	278.0	75	279.1	15.65	36.3	0.67	
AZT + 3TC	356	224.4	159	225.6	2.02	19.1	0.92	
2 other NRTIs	129	206.3	51	275.3	41.64	37.9	0.27	
Pre-specific								0.67
NVP	271	212.5	118	226.3	11.57	24.6	0.64	
EFV	324	245.8	156	270.4	25.24	20.8	0.23	

**Table 6****Risk of POD, Death, or CD4 < 200 cells/mm<sup>3</sup>  
by Selected Baseline Subgroups**

<b>Baseline Subgroup</b>	<b>PI + NRTIs</b>		<b>NNRTI + NRTIs</b>		<b>NNRTI vs. PI</b>		
	<b>N</b>	<b>Rate</b>	<b>N</b>	<b>Rate</b>	<b>HR</b>	<b>P-Value</b>	<b>Interaction P-Value</b>
CD4+ (cells/mm <sup>3</sup> )							0.91
<= 200	260	7.7	254	7.8	1.01	0.94	
> 200	210	5.4	209	5.4	0.98	0.94	
HIV-RNA (copies/mL)							0.07
< 100,000	199	5.9	195	4.3	0.73	0.15	
100,000 +	271	7.2	268	8.6	1.18	0.29	
POD CD4 composite							0.63
Prior AIDS	184	9.3	179	10.6	1.13	0.48	
NO POD CD4 <= 200	110	4.8	110	4.5	0.96	0.89	
CD4 > 200	176	5.4	174	4.6	0.86	0.52	
Age							0.25
< 40 years	277	6.8	262	5.9	0.87	0.43	
40 + years	193	6.5	201	7.7	1.17	0.40	
Gender							0.92
Male	363	6.5	367	6.6	1.01	0.96	
Female	107	7.2	96	7.0	0.97	0.91	
Race							0.23
Latino	83	8.4	77	5.6	0.66	0.20	
Black	255	7.6	249	7.6	1.01	0.97	
White/Other	132	4.2	137	5.6	1.34	0.27	
IV Drug Use							0.88
No	398	6.0	391	6.0	0.99	0.97	
Yes	72	10.6	70	10.0	0.94	0.82	
Hepatitis B							0.27
-	413	6.7	415	6.4	0.97	0.81	
+	25	8.7	26	14.6	1.53	0.35	
Hepatitis C							0.93
-	368	6.0	370	6.1	1.01	0.93	
+	101	9.5	91	9.3	0.98	0.95	
Baseline NRTI							0.70
Pre-specified AZT+3TC	222	6.1	239	6.5	1.06	0.76	
Other	248	7.1	224	6.8	0.96	0.79	
Baseline Drugs							0.02
Pre-specified NFV / EFV	157	5.1	167	8.0	1.55	0.05	
Other	313	7.5	296	6.0	0.81	0.17	

**Table 7**

**Time to Virologic Failure Associated With Drug Resistance**

	No. of events and rate per 100 person years						Hazard Ratio (95% Confidence Interval)		
	PI		NNRTI		PI + NNRTI		NNRTI vs. PI	(PI + NNRTI) vs. PI	(PI + NNRTI) vs. NNRTI
	N	Rate	N	Rate	N	Rate			
Virologic failure <sup>1</sup> (VF)	328	36.2	266	22.5	272	24.6	0.66 (0.56, 0.78)	0.70 (0.60, 0.83)	1.07 (0.91, 1.27)
VF with any drug resistance <sup>2</sup>	135	14.9	128	10.9	127	11.5	0.78 (0.62, 1.0)	0.80 (0.63, 1.02)	1.03 (0.80, 1.31)
VF with PI resistance	37	4.1	5	0.4	11	1.0	0.11 (0.04, 0.28)	0.25 (0.13, 0.49)	2.28 (0.79, 6.55)
VF with NNRTI resistance	18	2.0	113	9.6	106	9.6	5.18 (3.15, 8.52)	4.98 (3.02, 8.20)	0.97 (0.74, 1.26)
VF with NRTI resistance	121	13.3	63	5.4	39	3.5	0.43 (0.31, 0.58)	0.27 (0.19, 0.39)	0.65 (0.43, 0.96)
Number at risk	460		450		450				

<sup>1</sup> Virologic failure is defined as the first HIV-1 RNA level > 1000 copies/ml after four months of follow-up. Persons are at risk of virologic failure if at least one viral load measurement is available at or after the 4-month visit.

<sup>2</sup> Drug resistance is defined as definite resistance according to genotypic resistance testing at the time of virologic failure.

**Table 8**

**Mutations Present At First Virologic Failure**

		PI	NNRTI	PI + NNRTI	Overall	
<b>Class</b>	<b>Mutation</b>	<b>N</b>	<b>N</b>	<b>N</b>	<b>N</b>	<b>Percent<sup>2</sup></b>
<b>PI</b>	30N	24	2	4	30	40.5
	33 I / F	7	6	5	18	24.3
	46 I / L	7	4	1	12	16.2
	82 A / T	1	0	4	5	6.8
	84 V	1	0	3	4	5.4
	90 M	9	2	7	18	24.3
	Any mutation	42	13	19	74	100.0
<b>NNRTI</b>	100 I	0	6	5	11	4.4
	103 N	5	76	73	154	61.1
	106 A / M	2	14	8	24	9.5
	108 I	2	15	11	28	11.1
	181 C / I	4	30	27	61	24.2
	188 C / H / L	2	6	3	11	4.4
	190 A / S	6	15	18	39	15.5
	225 H	0	3	3	6	2.4
	230L	1	2	1	4	1.6
	Any mutation	20	119	113	252	100.0
<b>NRTI</b>	41 L	2	7	4	13	5.0
	44D	1	0	1	2	0.8
	62 V	6	5	1	12	4.6
	65 R	2	6	1	9	3.5
	67 N	4	3	5	12	4.6
	69 D	1	0	2	3	1.2
	70 R	4	0	2	6	2.3
	74 V	2	4	3	9	3.5
	75 I	1	5	0	6	2.3
	77 L	2	0	0	2	0.8
	115 F	1	0	0	1	0.4
	116 Y	1	0	0	1	0.4
	118 I	14	8	9	31	11.9
	151 M	1	2	0	3	1.2
	184 I / V	116	55	35	206	79.2
	210 W	1	3	2	6	2.3
	215 F / Y	4	5	3	12	4.6
	219 E / Q	2	1	1	4	1.5
	Any mutation	132	76	52	260	100.0
	Number with GART results	326	262	268	856	
Number with no GART results	2	4	4	10		
Number at risk <sup>1</sup>	460	450	450	1360		

<sup>1</sup> Virologic failure is defined as HIV-1 RNA level > 1000 copies/ml after four months of follow-up. Persons are at risk of virologic failure if at least one viral load measurement is available at or after the 4-month visit.

<sup>2</sup> Of those with a mutation within that class

**Table 9**

**Description of genotypic resistance test results at first virologic failure<sup>1</sup>**

	PI		NNRTI		PI + NNRTI	
	N	%	N	%	N	%
<b>No resistance<sup>2</sup></b>	<b>191</b>	<b>58.6</b>	<b>134</b>	<b>51.1</b>	<b>141</b>	<b>52.6</b>
All sensitive	174	53.4	116	44.3	128	47.8
Not all sensitive	17	5.2	18	6.9	13	4.9
<b>Single-class resistance</b>	<b>96</b>	<b>29.4</b>	<b>77</b>	<b>29.4</b>	<b>100</b>	<b>37.3</b>
PI	5	1.5	1	0.4	2	0.8
NNRTI	9	2.8	64	24.4	81	30.2
NRTI	82	25.2	12	4.6	17	6.3
<b>Multi-class resistance</b>	<b>39</b>	<b>12.0</b>	<b>51</b>	<b>19.5</b>	<b>27</b>	<b>10.1</b>
PI and NRTI	30	9.2	2	0.8	2	0.8
PI and NNRTI	0	0.0	0	0.0	5	1.9
NNRTI and NRTI	7	2.1	47	17.9	18	6.7
PI and NNRTI and NRTI	2	0.6	2	0.8	2	0.8
<b>Resistant to more than one</b>						
PI	14	4.3	3	1.1	7	2.6
NNRTI	14	4.3	100	38.2	94	35.1
NRTI	7	2.1	17	6.5	7	2.6
<b>No. with GART</b>	<b>326</b>	<b>100.0</b>	<b>262</b>	<b>100.0</b>	<b>268</b>	<b>100.0</b>

<sup>1</sup> Virologic failure is defined as HIV-1 RNA level > 1000 copies/ml after four months of follow-up. Persons are at risk of virologic failure if at least one viral load measurement is available at or after the 4-month visit.

<sup>2</sup> No drug resistance (N=456) or no genotypic resistance test results (N=10)

**Table 10**  
**Description of Antiretroviral Regimens**  
**At First Virologic Failure**

Regimen	PI		NNRTI		PI + NNRTI	
	N	%	N	%	N	%
On original treatment strategy	217	66.6	152	58.0	121	45.2
Not on original treatment strategy	109	33.3	110	42.0	147	54.8
On PI, not on NNRTI	0	0.0	11	4.2	36	13.4
On NNRTI, not on PI	14	4.3	0	0.0	23	8.6
On PI + NNRTI	3	0.9	2	0.8	0	0.0
On NRTIs only	13	4.0	13	5.0	3	1.1
Not on AR drugs	79	24.2	84	32.1	85	31.7
No. of persons	326		262		265	
<b>Not on AR Therapy At Failure</b>						
Days off AR therapy, median	83.0		89.0		80.0	
With drug resistance	67.0		73.5		62.0	
Without drug resistance	86.0		90.5		88.0	
No. of persons	79		84		85	

<sup>1</sup> Virologic failure is defined as HIV-1 RNA level > 1000 copies/ml after four months of follow-up. Persons are at risk of virologic failure if at least one viral load measurement is available at or after the 4-month visit.

**Table 11**

**Presence of Drug Resistance B y Antiretroviral Therapy Status  
At First Virologic Failure**

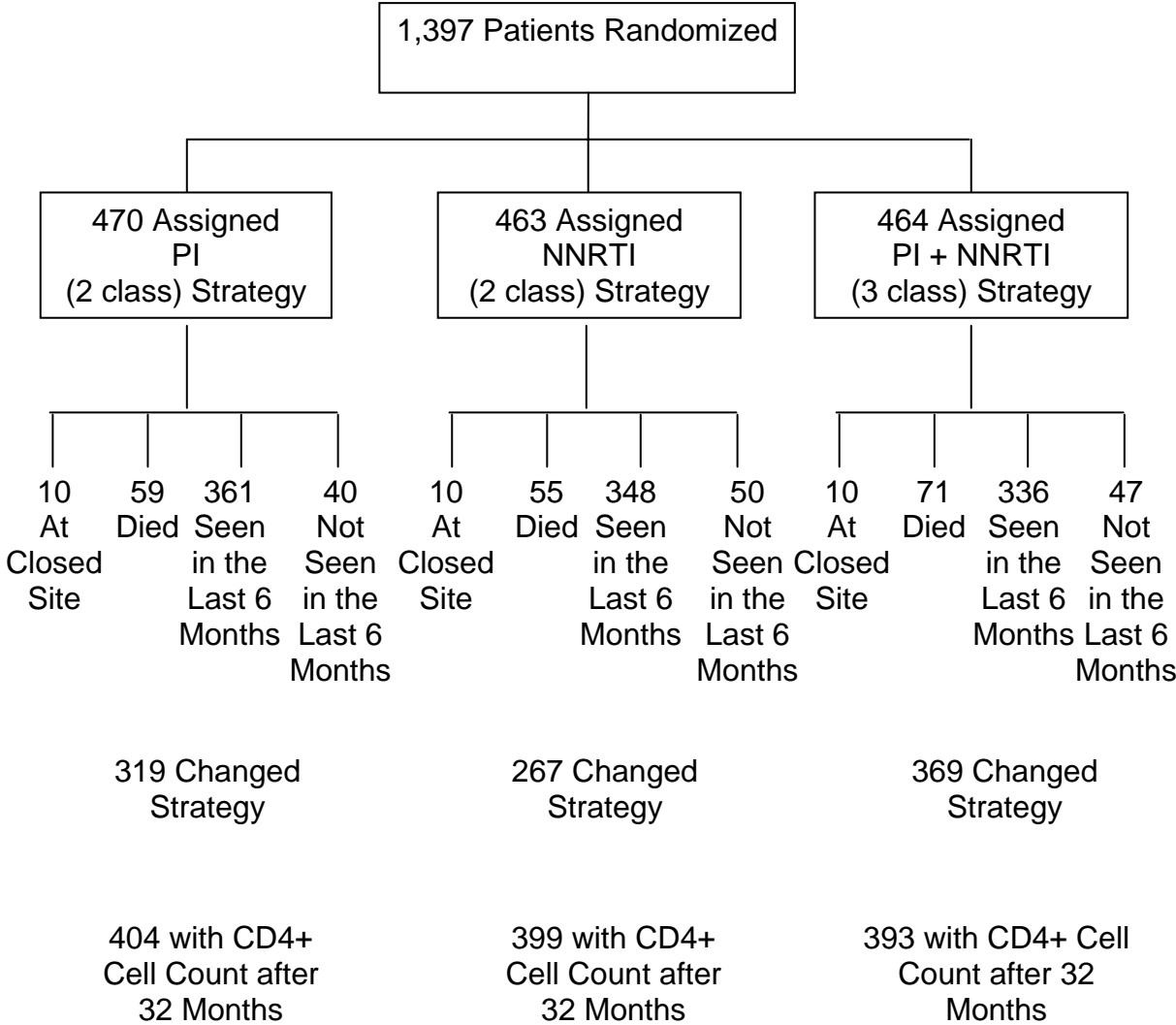
On antiretroviral therapy at failure?	PI Strategy			NNRTI Strategy			PI+NNRTI Strategy		
	No. of Pts	Drug Resistance		No. of Pts.	Drug Resistance		No. of Pts.	Drug Resistance	
		N	%		N	%		N	%
YES	247	125	50.6	178	108	60.7	183	106	57.9
NO	79	10	12.7	844	20	23.8	85	21	24.7
Overall	326	135	41.4	262	128	48.9	268	127	47.4

**Table 12**

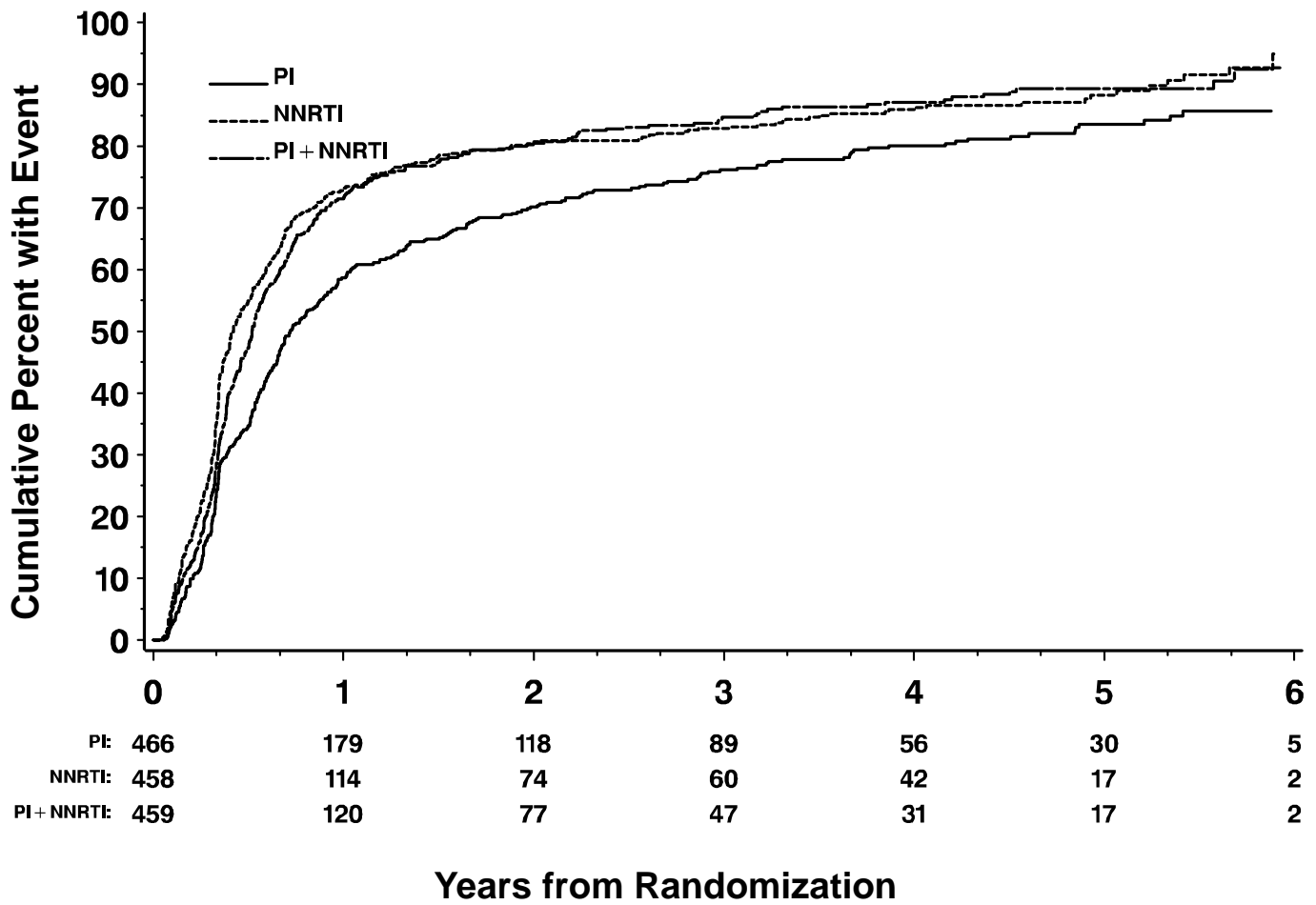
**Cross-Resistance Within a Class**

	<b>PI Strategy</b>		<b>NNRTI Strategy</b>		<b>3-class Strategy</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b>Within PI class</b>						
Nelfinavir only	23	62.2	2	40.0	4	36.4
Nelfinavir + other drugs	10	27.0	2	40.0	7	63.6
Ritonavir + Indinavir	4	10.8	1	20.0	0	0.0
No. pts with resistance to a PI drug	37	100.0	5	100.0	11	100.0
<b>Within NNRTI class</b>						
Efavirenz only	1	5.6	2	1.8	2	1.9
Nevirapine only	3	16.7	11	9.7	10	9.4
Nevirapine + Delavirdine	4	22.2	16	14.2	13	12.3
Efavirenz + Nevirapine + Delavirdine	10	55.6	84	74.3	81	76.4
No. pts. with resistance to a NNRTI drug	18	100.0	113	100.0	106	100.0
<b>Within NRTI class</b>						
3TC only	111	91.7	45	71.4	32	82.1
3TC + others	5	4.1	10	15.9	3	7.7
Other drugs	5	4.1	8	12.7	4	10.3
No. pts with resistance to a NRTI drug	121	100.0	63	100.0	39	100.0

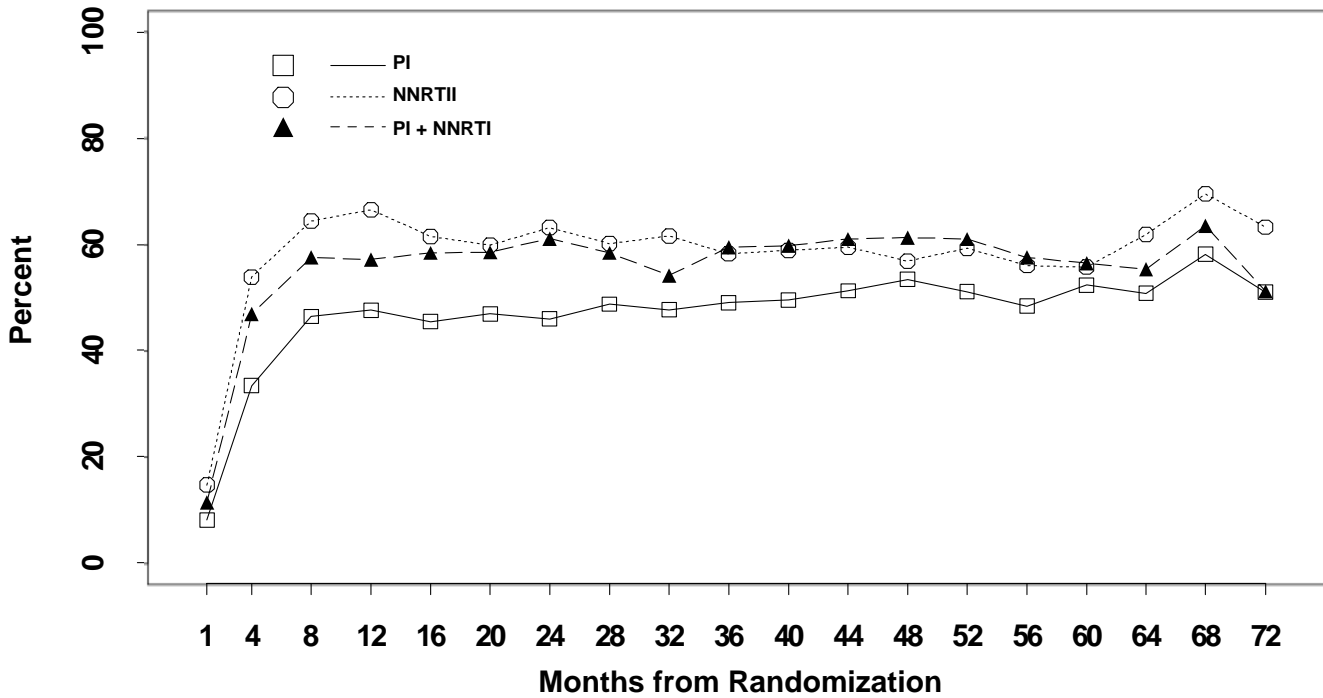
**Figure 1**  
**Flexible Initial Retrovirus Suppressive Therapies (FIRST)**



**Figure 2**  
**Time to First HIV-RNA < 50 copies/mL by Study Group**



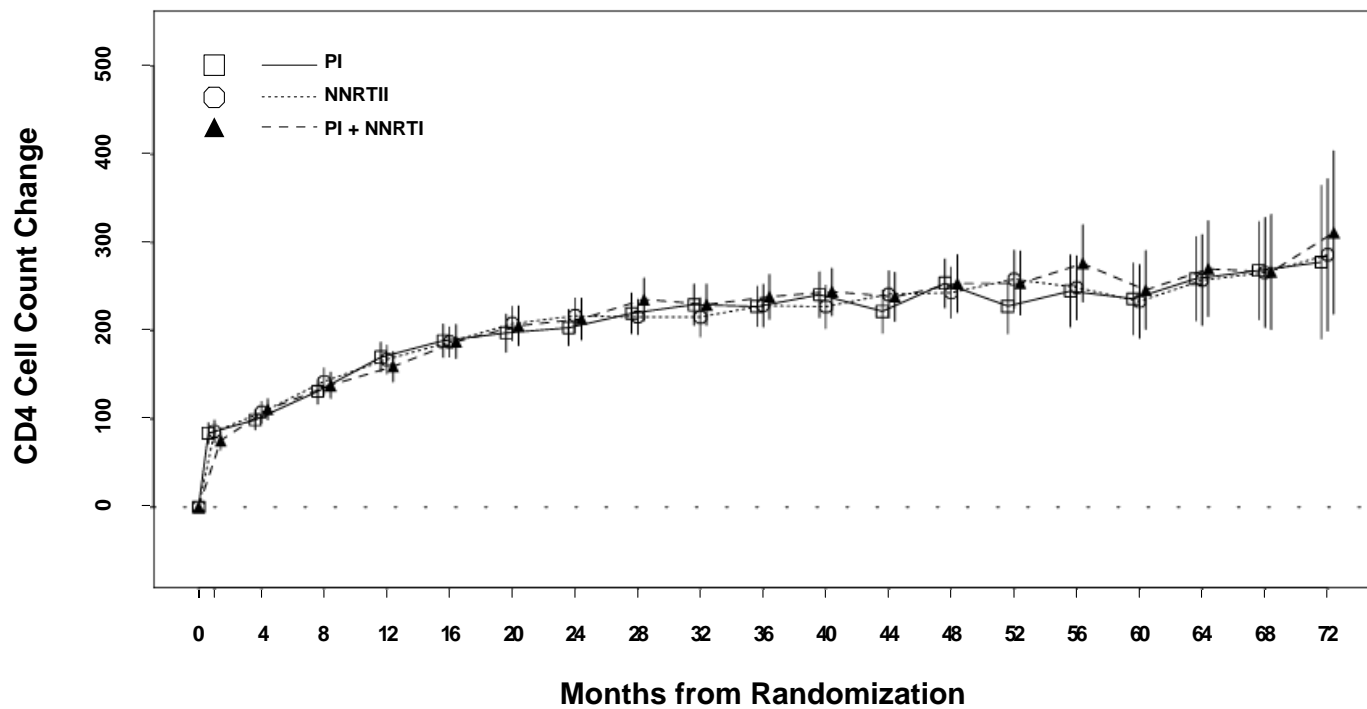
**Figure 3**  
**Percent of Patients with HIV RNA < 50 copies/mL by Study Group**



No. of Patients	
PI :	426 438 418 406 385 373 372 349 350 349 343 349 307 235 209 174 132 86 53
NNRTI :	440 429 410 392 390 376 377 354 354 354 355 321 292 253 216 165 118 82 49
PI+NNRTI :	434 426 412 404 387 374 370 356 345 341 326 313 287 244 198 147 112 74 43
p values:	0.01 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.01 0.01 0.02 0.15 0.06 0.13 0.72 0.21 0.31 0.38

\* Percentage is based on the number of patients who have a HIV RNA value at the specific time point

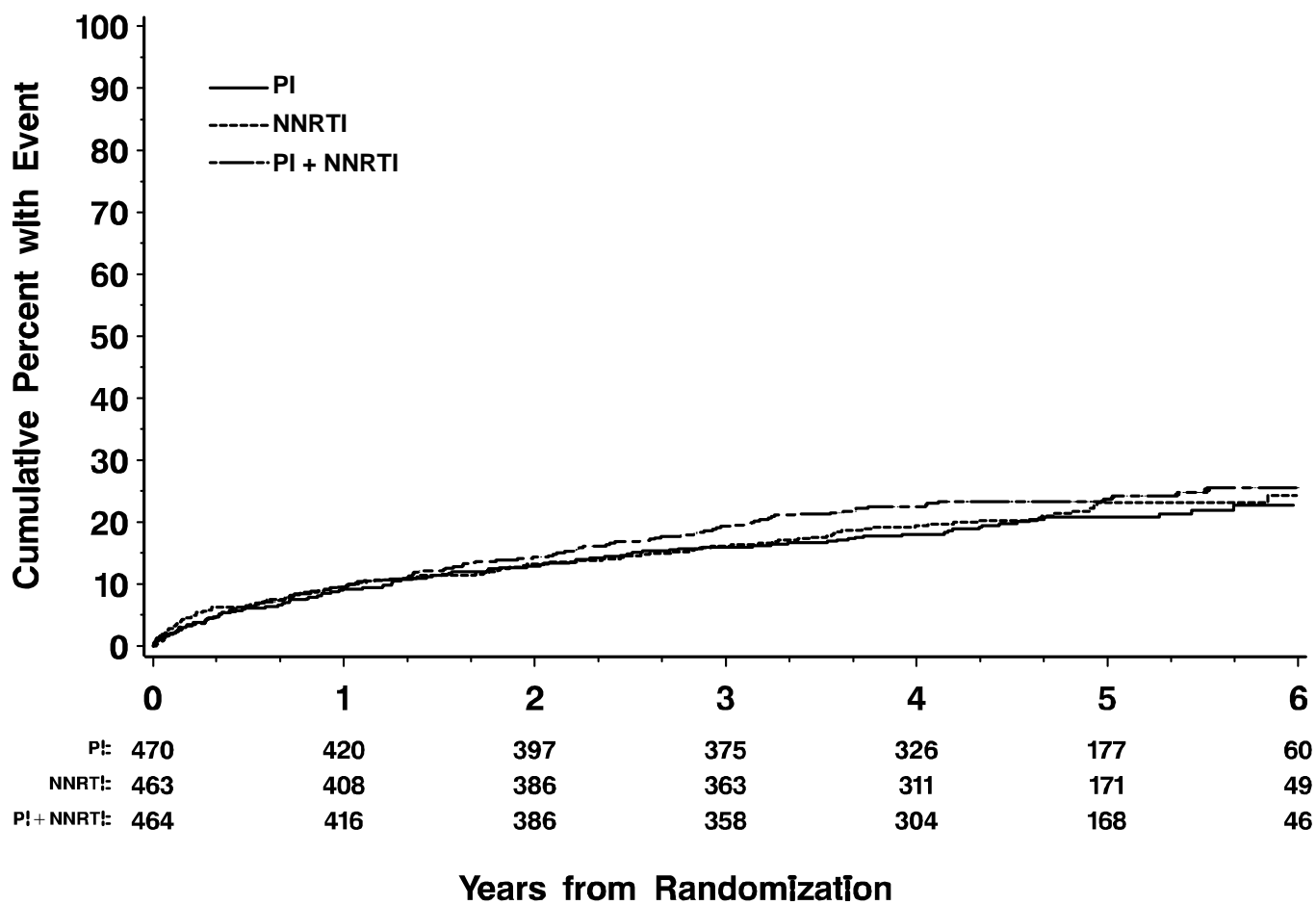
**Figure 4**  
**Mean Change (+, - 2SE) from Baseline in CD4 Cell Count (cells/mm<sup>3</sup>)**  
**by Study Group**



No. of Patients	
PI:	470 430 442 425 419 397 383 383 373 367 366 360 364 324 249 216 179 142 95 59
NNRTI:	463 440 434 414 398 393 385 386 369 368 367 363 339 307 267 232 182 130 89 50
PI+NNRTI:	464 438 429 418 406 395 383 379 374 361 363 344 330 299 258 210 162 126 81 53
p values*:	0.39 0.33 0.55 0.63 0.99 0.74 0.64 0.42 0.59 0.78 0.58 0.42 0.80 0.39 0.44 0.82 0.89 0.98 0.89

\* Adjusted for baseline value

**Figure 5**  
**Disease Progression or Death by Study Group**



## Appendix A

### NNRTI Substudy

#### INTRODUCTION

U.S. guidelines recommend efavirenz over nevirapine as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI). This recommendation is based on the larger body of evidence for efavirenz as compared to nevirapine that has established the superiority or equivalence of efavirenz with potent protease inhibitor (PI) regimens, and because of concerns about hepatic abnormalities with nevirapine. Head-to-head comparisons of efavirenz and nevirapine have not clearly established the superiority of one drug over the other with respect to 48-week virologic responses. There are few long-term data comparing the two drugs.

In the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study, participants could either elect to undergo a second randomization to efavirenz versus nevirapine (NNRTI substudy), or specify (prior to main-study randomization) the NNRTI to be used if they were assigned to the NNRTI + NRTIs or NNRTI + PI + NRTI strategies. This appendix describes the results of the NNRTI substudy.

#### METHODS

##### Study Design

Seventeen of the 18 participating clinical units in the FIRST study enrolled persons in the NNRTI substudy. Eligible persons who consented to the substudy were randomly allocated to efavirenz or nevirapine in a 1:1 allocation ratio. Randomization was stratified by clinical unit;

schedules were generated using randomly mixed permuted blocks of size 2 and 4. Assignments were obtained by calling a toll free number at the statistical center for CPCRA.

The primary objective of the NNRTI substudy of FIRST was to compare the rate of viral load  $> 50$  copies/mL at or after 8 months in the efavirenz and nevirapine groups. Since deaths could potentially lead to informative censoring, a composite outcome of a viral load  $> 50$  copies/mL at or after 8 months or death was used. Secondary objectives involved comparing the two NNRTIs for CD4+ cell count change, progression to AIDS or death and toxicities, including liver function changes, lipid changes, adherence, and the development of drug resistance.

### Study Subjects

HIV-infected persons were eligible if they met the eligibility criteria for the FIRST study, were 13 years of age or older, had not previously used a PI or NNRTI, had not used NRTI(s) for cumulative time of  $> 4$  weeks, and had not used 3TC for  $> 1$  week. Women of childbearing potential were required to use a barrier method of birth control to be eligible for the study.

### Data Collection

The protocol was approved by the local institutional review board of each site. Written informed consent was obtained from each participant both for the FIRST study and the NNRTI substudy.

Data collection procedures for the NNRTI substudy followed those for the FIRST study. Briefly, CD4+ cell counts were locally obtained at a screening visit and at the time of randomization (average is considered baseline); HIV RNA levels were obtained at the same time points and centrally determined using the Roche Ultrasensitive assay with a lower limit of

detection of 50 copies/mL. Following randomization, participants were seen at month 1, month 4, and every 4 months thereafter. At each visit, CD4+ cell count, HIV RNA, non-fasting blood lipids, glucose, AST, and ALT were measured, the participant's clinical status was assessed, (including side effects to treatment), and changes in ART and self-reported adherence were determined. Self-reported adherence was based on ART drugs prescribed in the 7 days prior to the follow-up visit. A genotypic resistance test was carried out at the first time HIV RNA was > 1000 copies/ml at or after the 4 month visit. Grade 4 (severe or life-threatening events) adverse events, including laboratory abnormalities, clinical signs and symptoms, diseases other than AIDS-defining events, and clinical syndromes were reported irrespective of the presumed relationship to ART and coded using a toxicity manual developed by the Division of AIDS and based on modified ICD-9 criteria. In addition to reporting any grade 4 event at each follow-up visit, selected side effects of any grade were assessed. In this report, cutaneous/rash/dermatitis and mood changes are described. Definitions for grade 1-4 cutaneous/rash/dermatitis were: Grade 1) erythema; pruritis; Grade 2) diffuse maculopapular rash or dry desquamation; Grade 3) vesiculation or moist desquamation or ulceration; Grade 4) exfoliative dermatitis or mucous membrane involvement or Stevens-Johnson syndrome or erythema multiforme or necrosis requiring surgery. Definitions for grade 3 and 4 moods (grade 1 and 2 were not defined) were: Grade 3) severe mood changes requiring medical intervention; Grade 4) acute psychosis requiring hospitalization.

### Sample Size

The primary endpoint for the NNRTI substudy was death or a viral load > 50 copies/mL at or after 8 months (virologic failure) of follow-up. Two hundred primary endpoints were

estimated to provide 80% power at the 0.05 significance level (2-sided) to detect a hazard ratio of 0.67 (efavirenz versus nevirapine). At the time the FIRST study was stopped, 187 events had occurred in the NNRTI substudy.

### Statistical Analyses

Most analyses were by intention to treat. Selected on-treatment analyses also have been performed excluding observations after the assigned NNRTI was discontinued. Time to event methods (e.g., Kaplan-Meier survival curves and Cox's proportional hazards model) were used to compare the efavirenz and nevirapine groups for the primary endpoint (death or viral load > 50 copies/mL at or after 8-month visit), progression to AIDS or death, grade 4 events, time to discontinuation of assigned NNRTI, and virologic failure associated with drug resistance. The censoring date used in the primary endpoint analyses was the date of the last centrally determined viral load. For other analyses the censoring date used was the closing date of the study (September 16, 2005) or the date the participant became lost to follow-up for the event considered. All of the analyses were stratified according to whether the participant was assigned the 2-class (NNRTI + NRTIs) or 3-class (NNRTI + PI + NRTI) strategy of FIRST.

Longitudinal regression models were used to compare CD4+ cell count levels, lipids, liver enzyme tests, and the percent of persons with a viral load < 50 copies/mL between the two treatment groups.

In comparing the two groups for rash and mental status changes, composite outcomes were created using a hierarchy of severity (e.g., grade 4 event; grade 4 event or discontinuation due to the event; grade 3 or 4 event or discontinuation due to the event; and any grade or discontinuation due to the event).

Statistical analyses were performed using SAS (Version 8.2). All p-values cited are 2-sided.

## RESULTS

Between March 1999 and January 2002, 228 persons were randomized, 117 to nevirapine and 111 to efavirenz (Figure A1).

The treatment groups were well balanced in terms of baseline characteristics (Table A1). The median age was 37 years; 23% of participants were female; and over 77% were non-white - 60% black and 17% Latino. Median HIV RNA level and CD4+ cell count were 143,396 copies/mL and 186 cells/mm<sup>3</sup>, respectively. Thirty-seven percent of participants reported a history of a prior AIDS event. Approximately 5% of persons were co-infected with hepatitis B (hepatitis B surface antigen positive) and 18% were co-infected with hepatitis C (hepatitis C IgG positive).

Forty-eight percent of persons were assigned to the 2-class strategy in the FIRST trial (NRTIs plus an NNRTI) and 52% were assigned to the 3-class strategy (PI + NRTI(s) + NNRTI). Among those assigned to the 3-class strategy, nelfinavir (NFV) was the most frequently used PI; overall, 26% of persons in the substudy were prescribed NFV (Table A2). The most common NRTI combinations used were abacavir (ABC) + lamivudine (30% for those assigned to nevirapine and 26% for those assigned efavirenz); didanosine (ddI) + stavudine (28% assigned to nevirapine and 25% assigned to efavirenz); and zidovudine + lamivudine (16% and 23%, respectively for nevirapine and efavirenz assignments). A single NRTI could be used among persons assigned to the 3-class strategy in FIRST and about 10% of the participants in each treatment group were prescribed a single NRTI.

### Follow-up and Adherence to Assigned Strategy

Median follow-up was 64 months. During the year prior to the close of the study on September 16, 2005, 84% of surviving persons assigned nevirapine and 90% assigned efavirenz had a viral load determined (Figure A1).

Seventy-five percent of persons in the nevirapine group and 74% of persons in the efavirenz group discontinued their assigned NNRTI treatment during follow-up. Most who discontinued their assigned NNRTI did not switch to an alternate NNRTI. Cumulative percents discontinuing their assigned NNRTI after 12, 24 and 36 months were 43%, 56%, and 65% for those assigned nevirapine; corresponding percents for those assigned efavirenz were 33%, 53%, and 64%, respectively ( $p=0.76$  for difference based on logrank test). The fraction of follow-up time on the assigned treatment was 52% for those assigned nevirapine and 55% for those assigned efavirenz.

Among the participants assigned to the 2-class strategy (no PI), 45% of persons assigned nevirapine and 29% assigned efavirenz initiated a PI ( $p=0.08$ ) (Table A3). Among those assigned to the 3-class strategy in FIRST, 61% of persons assigned nevirapine and 63% of those assigned efavirenz discontinued the PI ( $p=0.85$ ). More persons assigned nevirapine switched their PI than those assigned efavirenz (25% versus 12%;  $p=0.06$ ).

Self-reported adherence for persons prescribed ART was assessed at each follow-up visit and was very high. At most visits more than two-thirds of persons in each treatment group reported 100% adherence to their ART treatments. There was no difference in self-reported adherence among the nevirapine and efavirenz groups ( $p=0.35$ ).

## HIV RNA Levels and CD4+ Cell Counts During Follow-up

Time-to-event analysis indicated that the time to HIV RNA > 50 copies/mL after 8 months or death did not vary significantly among the nevirapine and efavirenz groups (Figure 2 and Table A4; p=0.59). At 12, 24 and 36 months the cumulative percent of persons with a viral load > 50 copies/mL or dead was 48.3%, 68.4%, and 74.6% for those assigned nevirapine; corresponding percents for those assigned efavirenz were 49.0%, 70.1%, and 75.7%. These percents were 41.8%, 62.5% and 67.0% for nevirapine, and 38.9%, 57.6%, and 62.8% for those assigned efavirenz based on an on-treatment analysis.

At 12 months, the duration of previous studies of these NNRTIs, the percent of persons with a viral load > 50 copies/mL was 45.1% for those assigned nevirapine and 51.0% for those assigned efavirenz. The percent with a viral load > 50 copies/mL or who discontinued their assigned treatment or with missing data at 12 months was 64.1% for those assigned nevirapine and 64.9% for those assigned efavirenz.

Longitudinal regression analysis indicated that the percent of persons with a viral load < 50 copies/mL was also similar for the two group throughout follow-up (Figure A2; p=0.24). At 8 months, 51.9% of persons assigned nevirapine and 57.6% assigned efavirenz had a viral load < 50 copies/mL.

On average, CD4+ cell counts did not differ significantly over follow-up (p=0.26; Figure A3). Average increases in CD4+ from baseline to 12 months were 147 and 143 cells/mm<sup>3</sup> for the nevirapine and efavirenz groups. Average increases over the entire follow-up period were 153 and 172 cells/mm<sup>3</sup>, respectively.

## Disease Progression Summary

Overall, 57 persons experienced a disease progression event or died, 23 on nevirapine and 34 on efavirenz (hazard ratio = 1.67; p=0.06; Table A4). A similar number of persons died in each treatment group (18 assigned nevirapine and 20 assigned efavirenz).

### Drug Resistance

One hundred and fifty-seven persons had a genotypic resistance test performed in conjunction with their first virologic failure (86 assigned nevirapine and 71 assigned efavirenz). A greater proportion of persons assigned nevirapine developed resistance than those assigned to efavirenz for each major class of drugs. This was most evident for NRTI resistance (29% versus 7%) (hazard ratio = 0.20; p<0.01; Table A5). The most common NRTI mutations for those assigned nevirapine were M184V (71% of those with an NRTI mutation), K65R (14%), and L74V (14%). These mutations occurred in 44%, 0.0%, and 11%, respectively, of persons failing on efavirenz.

### Adverse Events Summary

The rate of grade 4 adverse events was significantly lower among persons assigned efavirenz compared to those assigned nevirapine (hazard ratio = 0.55; p=0.02; Table A4). The most common grade 4 events were elevated liver function tests (8 assigned nevirapine and 7 assigned efavirenz) and anemia (7 assigned nevirapine and 3 assigned efavirenz).

Total cholesterol and non-fasting triglycerides increased slightly in both treatment groups (Table A6). There were no significant differences between those assigned nevirapine and those assigned efavirenz. Lipid differences were more apparent in on-treatment analyses (Table A6)

Overall, average AST changes were small and did not differ between treatment groups. Findings were similar for subgroups defined by gender and baseline CD4+ cell count (Tables A7a, A7b). In both groups, small average decreases were seen. The percent with AST or ALT levels > 10 upper limit of normal (ULN) (8.5% on nevirapine and 6.3% on efavirenz) and the percent > 5.0 ULN (11% and 14%) did not differ by treatment group. The percent of persons with grade 3 or 4 rash or discontinuing treatment due to rash was 16% for those assigned nevirapine and 10% for those assigned efavirenz (p=0.16).

## SUMMARY

The NNRTI substudy of FIRST opened in March 1999 and randomized 228 antiretroviral-naïve HIV-infected persons to initiate therapy with either a nevirapine-containing or an efavirenz-containing antiretroviral regimen. Major findings include:

- 1) The rate of viral load > 50 copies/mL after 8 months of followup or death did not differ significantly between the efavirenz and nevirapine groups; however, differences in the hazard of 25% or less cannot be ruled out.
- 2) Nevirapine was associated with more NNRTI and NRTI resistance than efavirenz at the time of virologic failure.
- 3) Grade 4 event rates were significantly higher in persons assigned to nevirapine than in those assigned to efavirenz.
- 4) There was a trend toward higher AIDS/death rates among those assigned to efavirenz compared to those assigned to nevirapine.

**Table A1**  
**Baseline Characteristics by Treatment Group**

<b>Characteristic</b>	<b>Nevirapine (N = 117)</b>	<b>Efavirenz (N = 111)</b>	<b>Total (N = 228)</b>
Age (years) (Median, IQR)	36 (31 – 43)	38 (33 – 44)	36.5 (31 – 43)
Female (%)	22.2	23.4	22.8
Race/Ethnicity			
Black (%)	59.8	59.5	59.6
Latino (%)	17.9	16.2	17.1
White (%)	19.7	22.5	21.1
Other (%)	2.6	1.8	2.2
Intravenous drug use (%)	18.1	15.3	16.7
Hepatitis B (%)	4.5	5.0	4.8
Hepatitis C (%)	16.2	20.7	18.4
Prior AIDS (%)	36.8	37.8	37.3
Baseline <sup>+</sup> CD4 <sup>+</sup> (cells/mm <sup>3</sup> ) (Median, IQR)	195.5 (18.5 – 352.0)	181.0 (38.0 – 370.5)	186.0 (33.0 – 359.5)
Baseline <sup>+</sup> HIV-RNA (copies/mL) (Median, IQR)	166,089 (48,737 – 456,808)	134,217 (25,532 – 413,681)	143,396 (35,313 – 449,325)
% HIV RNA < 100,000 copies/mL	42.7	45.0	43.9
Total serum cholesterol (Median, IQR)	161.0 (140.0 – 193.0)	159.0 (135.0 – 188.0)	160.5 (138.0 – 191.0)
Non-fasting triglycerides (Median, IQR)	122.0 (88.0 – 202.0)	124.0 (83.0 – 180.0)	123.0 (85.5 – 187.0)
NRTI substudy (%)	55.1	44.9	51.8
2-Class strategy (%)	49.6	46.8	48.2

+ Average of screening and baseline levels.

**Table A2****Other Antiretroviral Treatment (ART) Prescribed at Time of Randomization**

	<b>Nevirapine*</b> (N = 117)		<b>Efavirenz**</b> (N = 111)	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
<b>PI</b>				
NFV	31	26.5	29	26.1
Ritonavir - Boosted PI	16	13.7	15	13.5
Other PI(s)	12	10.3	14	12.6
No PI	58	49.6	53	47.7
<b>NRTI</b>				
AZT + 3TC	19	16.2	25	22.5
d4T + 3TC	14	12.0	11	9.9
ABC + 3TC	35	29.9	29	26.1
ddI + d4T	33	28.2	28	25.2
Other NRTIs	0	0.0	0	0.0
Single NRTI	11	9.4	12	10.8
No NRTI	3	2.6	3	2.7
No ART	1	0.9	2	1.8

\* One person took efavirenz and four persons did not take assigned nevirapine.

\*\* Two persons did not take assigned efavirenz.

**Table A3****Adherence to Assigned Treatment**

	<b>Nevirapine (N = 117)</b>		<b>Efavirenz (N = 111)</b>		<b>P-value</b>
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>	
<b>Overall</b>					
Switched to alternate NNRTI	3	2.6	4	3.6	0.65
Discontinued assigned NNRTI	85	72.6	77	69.7	0.59
<b>2-Class strategy</b>					
	58		52		
Switched to alternate NNRTI	2	3.4	1	1.9	0.63
Discontinued assigned NNRTI	41	70.7	36	69.2	0.87
Initiated PI	26	44.8	15	28.8	0.08
While on assigned NNRTI	1	1.7	1	1.9	0.94
Not on assigned NNRTI	25	43.1	14	26.9	0.08
Switched NRTI	43	74.1	40	76.9	0.74
While on assigned NNRTI	8	13.8	8	15.4	0.81
Not on assigned NNRTI	35	60.3	32	61.5	0.90
<b>3-Class strategy</b>					
	59		59		
Switched to alternate NNRTI	1	1.7	3	5.1	0.31
Discontinued assigned NNRTI	44	74.6	41	69.5	0.54
Discontinued PI	36	61.0	37	62.7	0.85
While on assigned NNRTI	9	15.3	9	15.3	1.00
Not on assigned NNRTI	27	45.8	28	47.5	0.85
Switched PI	15	25.4	7	11.9	0.06
While on assigned NNRTI	7	11.9	2	3.4	0.08
Not on assigned NNRTI	8	13.6	5	8.5	0.38
Switched NRTI	50	84.7	44	74.6	0.17
While on assigned NNRTI	18	30.5	10	16.9	0.08
Not on assigned NNRTI	32	54.2	34	57.6	0.71

**Table A4****Summary of Virologic and Clinical Responses**

	<b>Nevirapine (N = 117)</b>		<b>Efavirenz (N = 111)</b>		<b>Hazard Ratio (EFV / NVP) (95% CI)</b>	<b>P-value</b>
	<b>No.</b>	<b>Rate</b>	<b>No.</b>	<b>Rate</b>		
Viral Load > 50 copies/mL after 8 months	94	45.9	82	42.1	0.89 (0.66 – 1.19)	0.42
Viral Load > 50 copies/mL after 8 months or death	98	42.8	89	41.2	0.92 (0.69 – 1.23)	0.59
Progression to AIDS or death	23	4.4	34	7.4	1.67 (0.98 – 2.83)	0.06
Death	18	3.2	20	3.8	1.18 (0.62 – 2.23)	0.62
Grade 4 Event	43	10.2	24	5.4	0.55 (0.33 – 0.90)	0.02
Progression to AIDS or Death or Grade 4 events	52	12.7	43	10.5	0.86 (0.57 – 1.28)	0.45

**Table A5****First Virologic Failure Associated with Drug Resistance**

	<u>Nevirapine (N = 117)</u>		<u>Efavirenz (N = 111)</u>		<u>Hazard Ratio (95% CI)</u>	<u>P-value</u>
	<u>No.</u>	<u>Rate</u>	<u>No.</u>	<u>Rate</u>		
<b><u>Drug Resistance at VF*</u></b>						
NNRTI	49	20.6	32	12.9	0.65 (0.41 – 1.01)	0.05
NRTI	25	10.5	5	2.0	0.20 (0.08 – 0.52)	0.00
Any PI / NNRTI / NRTI	54	22.7	33	13.3	0.60 (0.39 – 0.93)	0.02
<hr/>						
Number of persons with virologic failure	86		71			

\* First occurrence at or after month 4 visit.  
Relative risk and associated p-values are based on proportional hazards regression model stratified by 2 or 3 class. Rates are per 100 person-years.

**Table A6**  
**Change in Blood Lipids, Glucose and Insulin by**  
**Treatment Group**  
**(Intent-to-Treat Analyses)**

	Nevirapine (N = 117)		Efavirenz (N = 111)		Diff	SE	P-Value
	No.	Mean Change	No.	Mean Change			
Total serum cholesterol (mg/dl)	116	17.3	109	25.1	5.5	4.2	0.19
Non-fasting triglycerides (mg/dl)	116	12.8	109	32.6	14.5	11.4	0.21
<u>Fasting Lipids*</u>							
Total cholesterol (mg/dl)	47	21.9	40	21.2	5.4	6.7	0.42
Triglycerides (mg/dl)	47	11.6	40	60.0	59.4	19.2	0.00
LDL cholesterol (mg/dl)	46	11.1	40	3.4	-6.0	5.7	0.29
HDL cholesterol (mg/dl)	46	7.4	40	6.9	1.3	2.4	0.58
Glucose (mg/dl)*	47	4.4	40	7.0	5.0	3.5	0.16
Insulin (mL)*	47	3.7	40	1.0	0.5	2.4	0.84

\* Metabolic substudy (CPCRA 061) patients only

**Table A6 (continued)**  
**Change in Blood Lipids, Glucose and Insulin by**  
**Treatment Group**  
**(On-Treatment Analyses)**

	Nevirapine (N = 117)		Efavirenz (N = 111)		Diff	SE	P-Value
	No.	Mean Change	No.	Mean Change			
Total serum cholesterol (mg/dl)	103	25.8	99	32.3	5.7	4.6	0.22
Non-fasting triglycerides (mg/dl)	103	9.3	99	41.7	22.5	14.0	0.11
<u>Fasting Lipids*</u>							
Total cholesterol (mg/dl)	47	21.9	40	21.2	5.4	6.7	0.42
Triglycerides (mg/dl)	47	11.6	40	59.9	59.4	19.2	0.00
LDL cholesterol (mg/dl)	46	11.1	40	3.4	-6.0	5.7	0.29
HDL cholesterol (mg/dl)	46	7.4	40	6.9	1.3	2.4	0.58
Glucose (mg/dl)*	47	4.4	40	7.0	5.0	3.5	0.16
Insulin (mL)*	47	3.7	40	1.0	0.5	2.4	0.84

\* Metabolic substudy (CPCRA 061) patients only

**Table A7a****Liver Enzyme Changes by Treatment Group:  
Overall and According to Baseline CD4+ Cell Count and Gender****(Intent-to-Treat Analyses)**

	<u>Nevirapine</u>		<u>Efavirenz</u>		<u>Diff</u>	<u>SE</u>	<u>P-Value</u>
	<u>No.</u>	<u>Mean Change</u>	<u>No.</u>	<u>Mean Change</u>			
<b><u>AST</u></b>							
Overall	116	-3.11	110	-3.47	1.6	4.2	0.71
<b><u>Baseline CD4+</u></b>							
≤ 250	71	-3.0	61	-6.8	2.7	6.0	0.65
> 250	45	-3.2	49	0.6	2.2	5.2	0.67
<b><u>Gender</u></b>							
Men	90	-3.9	84	-3.1	2.6	5.1	0.61
Women	26	-0.2	26	-4.6	-3.1	6.1	0.61
<b><u>ALT</u></b>							
Overall	116	-1.90	110	-2.46	1.4	4.0	0.72
<b><u>Baseline CD4+</u></b>							
≤ 250	71	-1.6	61	-5.7	-0.8	5.4	0.88
> 250	45	-2.4	49	1.5	4.8	5.7	0.39
<b><u>Gender</u></b>							
Men	90	-1.6	84	-1.5	2.0	4.8	0.68
Women	26	-2.9	26	-5.5	0.1	6.6	0.99

**Table A7a (continued)**

**Liver Enzyme Changes by Treatment Group:  
Overall and According to Baseline CD4+ Cell Count and Gender**

**(On-Treatment Analyses)**

	<u>Nevirapine</u>		<u>Efavirenz</u>		<u>Diff</u>	<u>SE</u>	<u>P-Value</u>
	<u>No.</u>	<u>Mean Change</u>	<u>No.</u>	<u>Mean Change</u>			
<b><u>AST</u></b>							
Overall	103	-1.9	99	-6.0	-2.7	4.8	0.58
<b><u>Baseline CD4+</u></b>							
≤ 250	61	-5.4	54	-12.6	0.5	6.3	0.94
> 250	42	3.3	45	1.9	-3.6	7.3	0.62
<b><u>Gender</u></b>							
Men	81	-4.1	77	-6.5	-1.1	5.5	0.83
Women	22	6.3	22	-4.2	-10.0	8.4	0.23
<b><u>ALT</u></b>							
Overall	103	0.9	99	3.9	2.3	7.3	0.75
<b><u>Baseline CD4+</u></b>							
≤ 250	61	-1.1	54	-6.4	-2.8	6.0	0.64
> 250	42	3.8	45	16.3	11.4	17.9	0.53
<b><u>Gender</u></b>							
Men	81	-0.2	77	7.7	4.9	9.0	0.59
Women	22	4.8	22	-5.9	-8.2	9.3	0.38

**Table A7b**

**Selected Adverse Events by Severity and Treatment Group**

**(Intent-to-Treat Analyses)**

	<b>Nevirapine (N = 117)</b>		<b>Efavirenz (N = 111)</b>		<b>P-value</b>
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>	
<b><u>AST or ALT</u></b>					
> 2.5 ULN at least once during fu	38	32.8	30	27.3	0.37
> 5 ULN at least once during fu	13	11.2	15	13.6	0.58
> 10 ULN at least once during fu or Grade 4 AE	10	8.5	7	6.3	0.52
<b><u>Rash</u></b>					
Grade 4	0	0.0	0	0.0	--
Grade 4 or discontinued due to rash	10	8.5	4	3.6	0.12
Grade 3* or 4 or discontinued due to rash	19	16.2	11	9.9	0.16
Grade 4 or discontinued due to rash or rash of any grade from symptom severity	77	65.8	74	66.7	0.89
<b><u>Mental Status Change (MSC)</u></b>					
Grade 4	4	3.4	2	1.8	0.45
Grade 4 or discontinued due to MSC	5	4.3	9	8.1	0.23
Grade 3* or 4 or discontinued due to MSC	46	39.3	38	34.2	0.43

Note: Discontinued due to rash (or MSC) of any grade.

\* From symptom severity form.

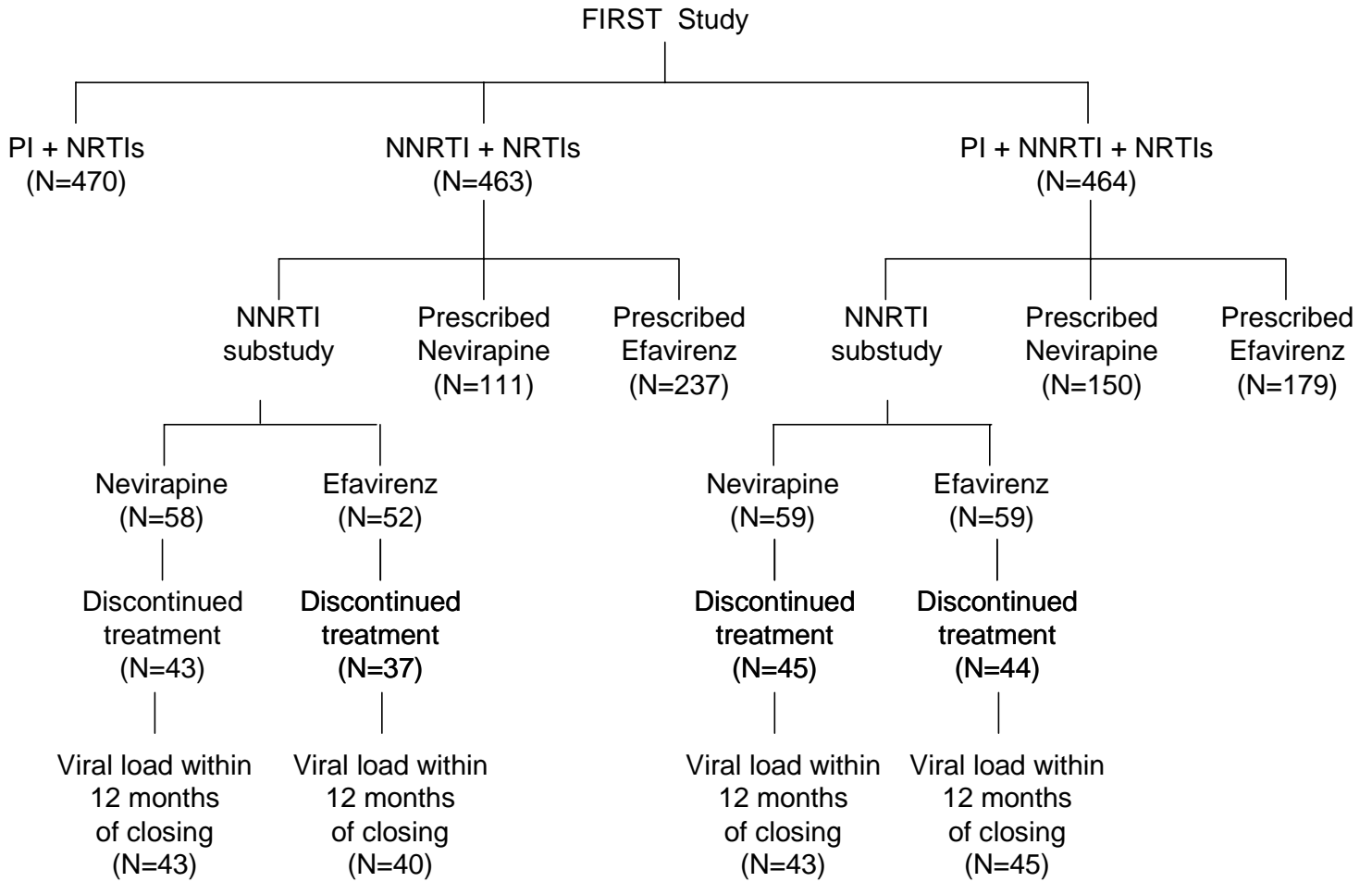
**Table A7b (continued)**  
**Selected Adverse Events by Severity and Treatment Group**  
**(On-Treatment Analyses)**

	Nevirapine (N = 117)		Efavirenz (N = 111)		P-value
	No.	%	No.	%	
<b><u>AST or ALT</u></b>					
> 2.5 ULN at least once during fu	22	19.0	21	19.4	0.93
> 5 ULN at least once during fu	8	6.9	8	7.4	0.88
> 10 ULN at least once during fu or grade 4 AE	6	5.1	3	2.7	0.35
<b><u>Rash</u></b>					
Grade 4	0	0.0	0	0.0	--
Grade 4 or discontinued due to rash	7	6.0	3	2.7	0.23
Grade 3* or 4 or discontinued due to rash	12	10.3	6	5.4	0.18
Grade 4 or discontinued due to rash or rash of any grade from symptom severity	57	48.7	52	46.8	0.78
<b><u>Mental Status Change (MSC)</u></b>					
Grade 4	1	0.9	0	0.0	0.33
Grade 4 or discontinued due to MSC	1	0.9	6	5.4	0.05
Grade 3* or 4 or discontinued due to MSC	25	21.4	26	23.4	0.71

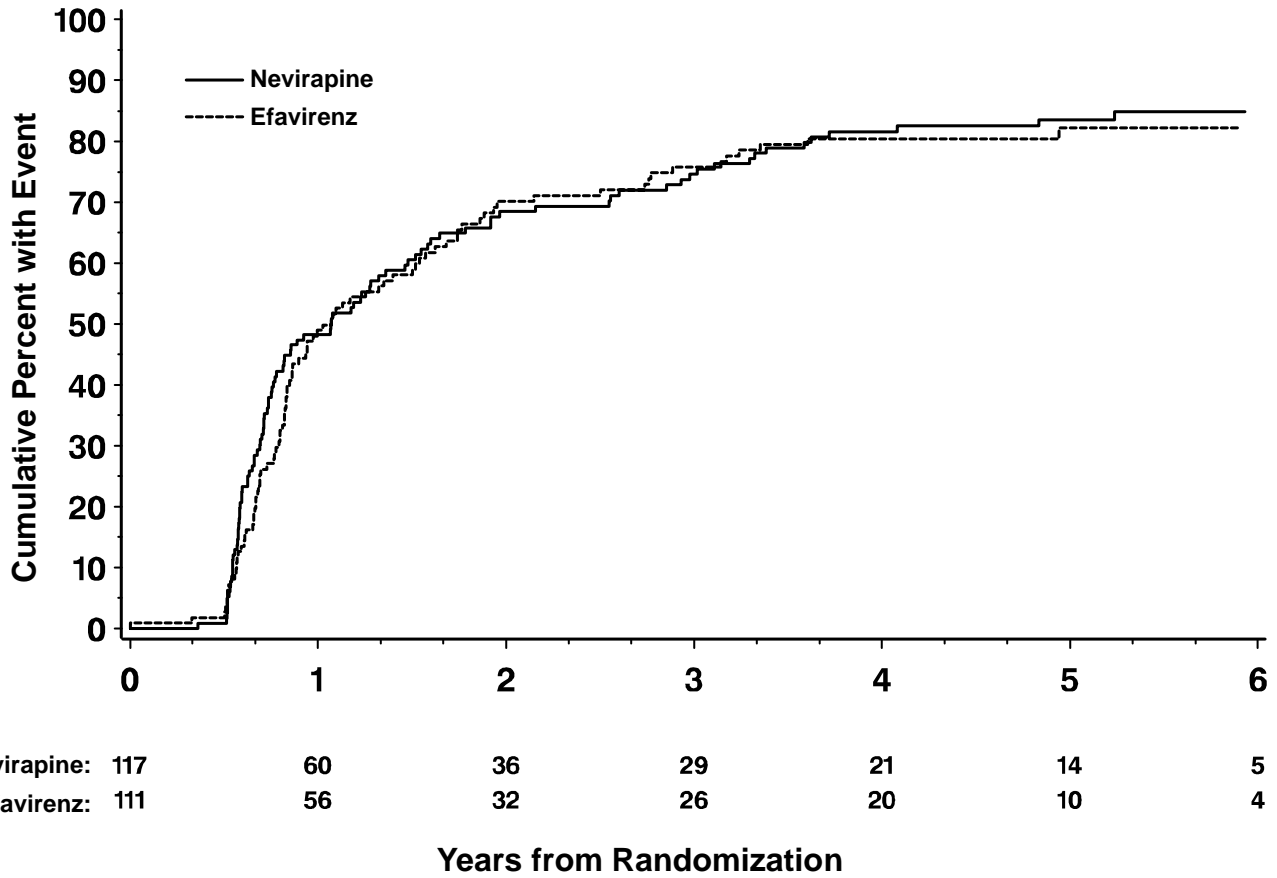
Note: Discontinued due to rash or MSC are of any grade.

\* From symptom severity form.

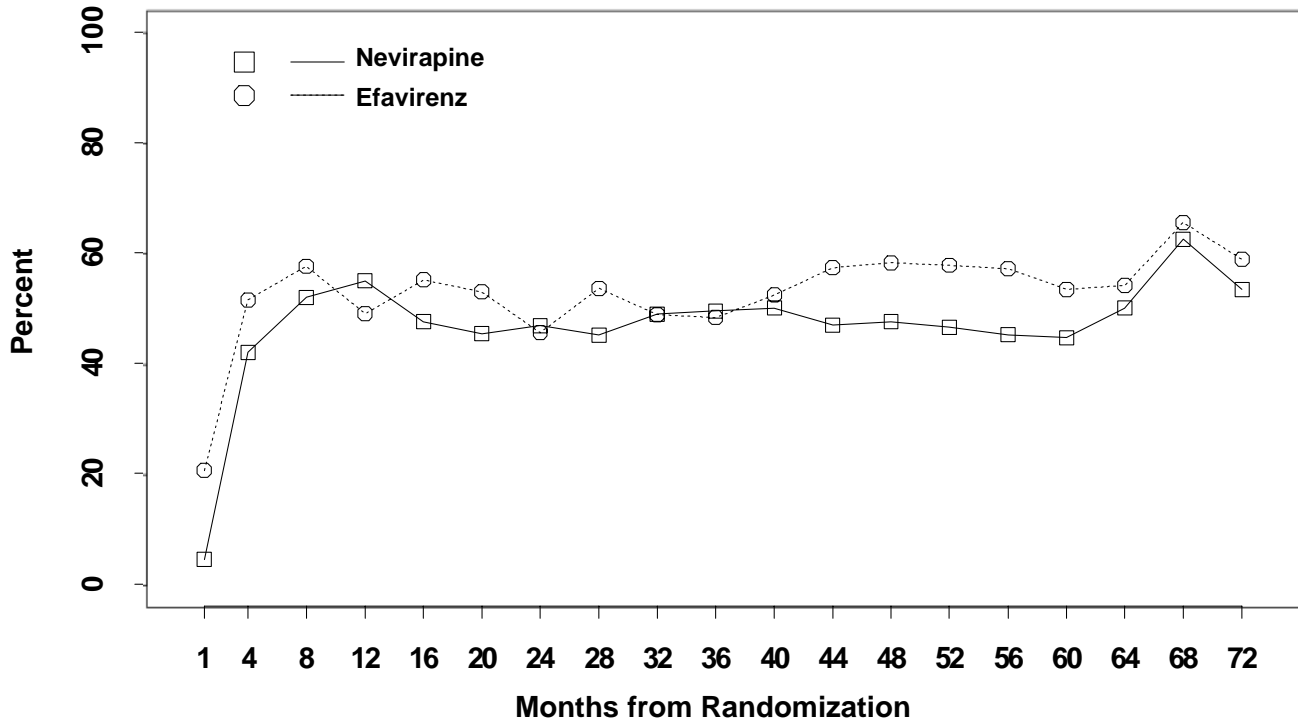
## Figure A1 NNRTI Substudy



**Figure A2**  
**Time to Death or First HIV > 50 copies/mL at or after Month 8 Visit**  
**by Treatment Group**



**Figure A3**  
**Percent of Patients with HIV RNA < 50 copies/mL by Treatment Group**

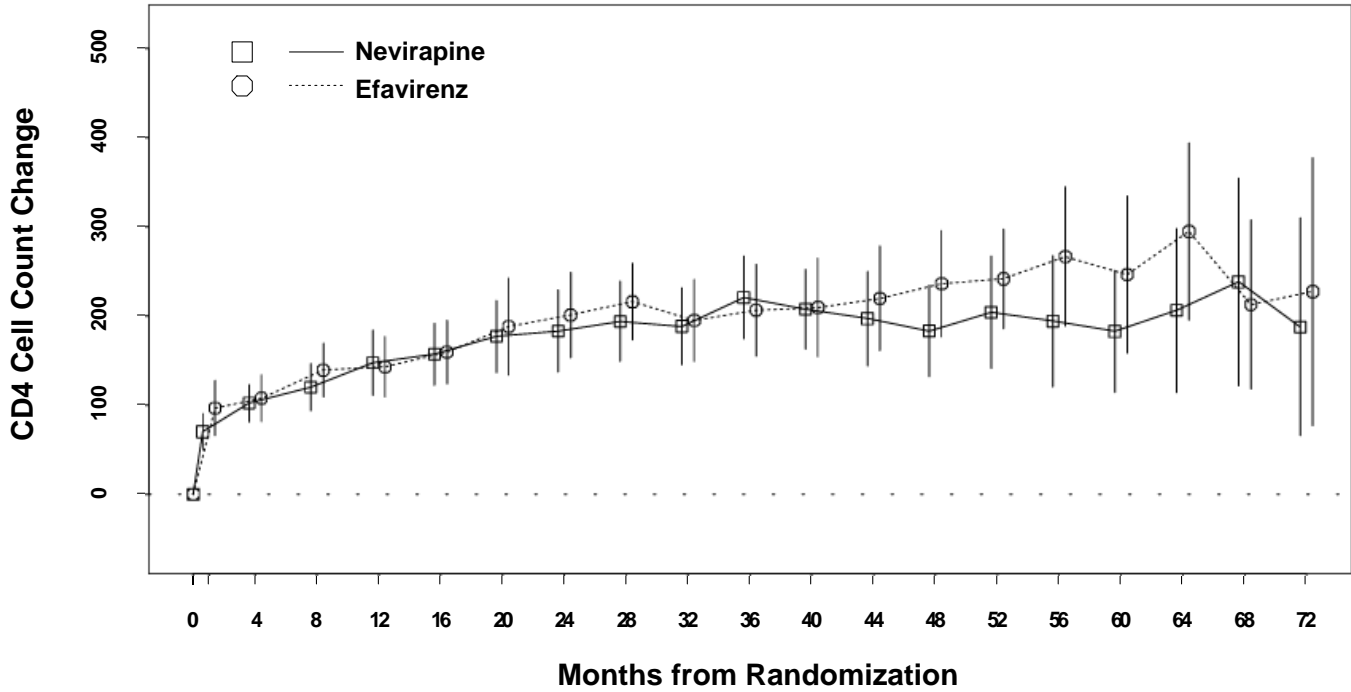


No. of Patients

Nevirapine:	112	112	104	102	101	97	94	91	88	89	86	81	82	73	62	56	42	24	15
Efavirenz:	102	101	99	96	89	87	90	84	86	85	86	82	79	71	63	45	37	29	17
p values:	0.000	0.16	0.42	0.40	0.30	0.31	0.86	0.26	1.00	0.87	0.76	0.18	0.18	0.18	0.18	0.39	0.72	0.82	0.75

\* Percentage is based on the number of patients who have a HIV RNA value at the specific time point

**Figure A4**  
**Mean Change (+ - 2SE) from Baseline in CD4 Cell Count (cells/mm<sup>3</sup>)**  
**by Treatment Group**



No. of Patients

Nevirapine:	117	112	112	103	104	102	97	97	94	89	94	90	84	86	79	63	59	43	27	18
Efavirenz:	111	103	100	99	95	90	88	92	91	89	86	88	86	81	72	67	50	40	30	19

p values\*: 0.16 0.84 0.44 0.86 0.92 0.72 0.57 0.47 0.85 0.65 0.99 0.60 0.21 0.49 0.17 0.21 0.19 0.91 0.72

\* Adjusted for baseline value

## Appendix B

### PI Substudy

#### INTRODUCTION

At the time the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study was initiated, there were limited data on the comparative efficacy of nelfinavir (NFV), indinavir (IDV) and double protease inhibitor (PI) regimens (i.e., ritonavir (RTV)-boosted). In the FIRST study, participants could specify (prior to main-study randomization) the PI to be used if they were assigned to the PI or PI + NNRTI strategies or elect to undergo a second randomization to NFV, IDV, or a double PI regimen of the participant/clinician's choice. This appendix describes the results of the PI substudy.

#### METHODS

##### Study Design

Fifteen of the 18 participating clinical units in the FIRST study enrolled persons in the PI substudy. Eligible persons who consented to the substudy were randomly allocated to NFV, IDV or to a double PI in a 1:1:1 allocation ratio. Randomization was stratified by clinical unit; schedules were generated using randomly mixed permuted blocks of size 3 and 6. Assignments were obtained by calling a toll free number at the statistical center for CPCRA.

The primary objective of the PI substudy of FIRST was to compare the rate of viral load > 50 copies/mL at or after 8 months in the three PI groups. Since deaths could potentially lead to informative censoring, a composite outcome of a viral load > 50 copies/mL at or after 8 months or death was used. Secondary objectives involved comparing the three PI-based regimens for

CD4+ cell count change, progression to AIDS or death and toxicities, including liver function changes, lipid changes, adherence and drug resistance.

### Study Subjects

HIV-infected persons were eligible if they met the eligibility criteria for the FIRST study, were 13 years of age or older, had not previously used a PI or NNRTI, had not used NRTI(s) for cumulative time of > 4 weeks, and had not used 3TC for > 1 week. Women of childbearing potential were required to use a barrier method of birth control to be eligible for the study. In addition, participants had to be randomized to one of the arms of FIRST that required use of a PI.

### Data Collection

The protocol was approved by the local institutional review board of each site. Written informed consent was obtained from each participant both for the FIRST study and the PI substudy.

Data collection procedures for the PI substudy followed those for the FIRST study. Briefly, CD4+ cell counts were locally obtained at a screening visit and at the time of randomization (average is considered baseline); HIV RNA levels were obtained at the same time points and centrally determined using the Roche Ultrasensitive assay with a lower limit of detection of 50 copies/mL. Following randomization, participants were seen at month 1, month 4, and every 4 months thereafter. At each visit, CD4+ cell count, HIV RNA, non-fasting blood lipids, glucose, AST, and ALT were measured, the participant's clinical status was assessed, (including side effects to treatment), and changes in ART and self-reported adherence were determined. Self-reported adherence was based on ART drugs prescribed in the 7 days prior to

the follow-up visit. A genotypic resistance test was performed the first virologic failure, defined as viral load > 1,000 copies/mL after 4 months of follow-up.

Grade 4 (severe or life-threatening events) adverse events, including laboratory abnormalities, clinical signs and symptoms, diseases other than AIDS-defining events, and clinical syndromes, were reported irrespective of the presumed relationship to ART and coded using a toxicity manual developed by the Division of AIDS and based on modified ICD-9 criteria.

### Sample Size

The primary endpoint for the PI substudy was death or a viral load > 50 copies/mL at or after 8 months (virologic failure) of follow-up. One hundred and forty primary endpoints were estimated to provide 80% power at the 0.017 significance level (2-sided adjusted for 3 planned pairwise comparisons) to detect a hazard ratio of 0.50 between any pair of the PI regimens. At the time the FIRST study was stopped, 146 events had occurred in the PI substudy.

### Statistical Analyses

Most analyses are by intention to treat. Selected on-treatment analyses also have been performed excluding observations after the assigned PI was changed. Time to event methods (e.g., Kaplan-Meier survival curves and Cox's proportional hazards model) are used to compare the three PI groups for the primary endpoint (death or viral load > 50 copies/mL at or after 8 months), progression to AIDS or death, grade 4 events, time to change of assigned PI, and virologic failure associated with drug resistance. The censoring date used in the primary endpoint analyses was the date of the last centrally determined viral load. For other analyses the

censoring date used was the closing date of the study (September 16, 2005) or the date the participant became lost to follow-up for the event considered. All of the analyses are stratified according to whether the person was assigned the 2-class (PI + NRTI) or 3- class (PI + NNRTI + NRTI) of FIRST.

Longitudinal regression models were used to compare CD4+ cell count levels, lipids, and live enzyme tests, and the percent of persons with a viral load < 50 copies/mL among the 3 treatment groups.

Statistical analyses were performed using SAS (Version 8.2). P-values are cited corresponding to omnibus (2 degree of freedom) tests and to pair-wise comparisons.

## RESULTS

Between February 1999 and January 2002, 167 persons were randomized, 58 to IDV, 56 to NFV, and 53 to a double PI of choice (Figure B1); 40% of the persons assigned IDV, 34% of those assigned NFV, and 49% of those assigned a double PI participated in the metabolic substudy of FIRST. Among persons assigned to the double PI group, the most common PI combinations were IDV+RTV (50.9%); saquinavir (SQV) + RTV (26.4%); and lopinavir (LPV) + RTV (13.2%).

The treatment groups were well balanced in terms of demographic and other baseline characteristics (Table B1). The median age was 37 years; 22% of participants were female; and over 79% were non-white -- 62% black and 15% Latino. Median CD4+ cell count was 197 cells/mm<sup>3</sup>. Approximately 35% of participants reported a history of a prior AIDS event; 6% of persons were co-infected with hepatitis B (hepatitis B surface antigen positive) and 23% were co-infected with hepatitis C (hepatitis C IgG positive).

Forty-eight percent of participants were assigned to the 2-class strategy in the FIRST trial (PI + NRTIs) and 52% were assigned to the 3-class strategy (PI + NRTI(s) + NNRTI). Among those assigned to the 3-class strategy, nevirapine was prescribed for 50.6% of persons and efavirenz was prescribed for 46% of persons. The most common NRTI combinations used were abacavir (ABC) + lamivudine (3TC) (27.6%, 26.8%, and 32.1% for those assigned IDV, NFV, and the double PI, respectively); didanosine (ddI) + stavudine (d4T)(22.4%, 26.8% and 26.4% for IDV, NFV, and double PI, respectively); and zidovudine + lamivudine (20.7%, 23.2% and 15.1%, respectively). A single NRTI could be used among persons assigned to the 3-class strategy in FIRST and 14.8%, 12.9%, and 20.7%, respectively, of the persons in the 3-class strategy arm of FIRST who were randomly assigned IDV, NFV, and the double PI, respectively, were prescribed a single NRTI (Table B2).

#### Follow-up and Adherence to Assigned Strategy

Median follow-up was 65.8 months. During the year prior to the close of the study on September 16, 2005, 93% of surviving persons assigned IDV, 86% assigned NFV, and 91% assigned a double PI had a viral load determined (Figure B1).

Seventy-nine percent of persons in the IDV group, 82% in the NFV group, and 87% in the double PI group discontinued their assigned PI treatment during follow-up. Most who discontinued their assigned PI did not switch to an alternate PI. Cumulative percents discontinuing their assigned PI after 12, 24 and 36 months were 39.8%, 57.8%, and 72.5% for those assigned IDV; 33.9%, 60.7%, and 71.4% for those assigned NFV; and 45.3%, 60.4%, and 64.2% for those assigned a double PI (p=0.71 for difference among groups based on logrank

test). The fraction of follow-up time on the assigned treatment was 41% for those assigned IDV, 49% for those assigned NFV, and 52% for those assigned a double PI.

Among the participants assigned to the 2-class strategy (no NNRTI), 45% of persons assigned IDV, 28% assigned NFV and 50% assigned a double PI initiated an NNRTI ( $p=0.26$ ) (Table B3). Among those assigned to the 3-class strategy in FIRST, 78% of persons assigned IDV, 77% assigned NFV, and 72% of those assigned a double PI discontinued the NNRTI ( $p=0.87$ ).

Self-reported adherence for participants prescribed ART was assessed at each follow-up visit and was very high. At most visits more than two-thirds of persons in each treatment group reported 100% adherence to their ART treatments. Differences in self-reported adherence among the three treatment groups were not significant ( $p=0.15$ ).

#### HIV RNA Levels and CD4+ Cell Counts During Follow-up

Time-to-event analysis indicated that the time to HIV RNA > 50 copies/mL after 8 months or death did not vary significantly among the 3 PI groups (Figure B2 and Table B4;  $p=0.50$ ). At 12, 24 and 36 months the cumulative percent of persons with a viral load > 50 copies/mL or dead was 69.0%, 82.8%, and 89.7%, respectively, for those assigned IDV; 51.8%, 81.0%, and 81.0%, respectively, for those assigned NFV; and 52.8%, 75.5%, and 79.3%, respectively, for those assigned a double PI. These percents were 67.6%, 76.6% and 85.0%, respectively, for IDV; 50.9%, 75.9%, and 75.9%, respectively, for those assigned NFV; and 40.5%, 68.5%, and 72.0%, respectively, for those assigned a double PI based on a on-treatment analysis.

Longitudinal regression analysis indicated that the percent of persons with a viral load < 50 copies/mL was also similar for the 3 groups throughout follow-up (Figure B3;  $p=0.60$ ). At 8 months, 44.7% of persons assigned IDV, 53.2% assigned NFV, and 53.1% assigned a double PI had a viral load < 50 copies/mL.

On average, CD4+ cell counts did not differ significantly over follow-up ( $p=0.87$ ; Figure B4). Average increases in CD4+ from baseline to 12 months were 116, 171 and 152 cells/mm<sup>3</sup> for the IDV, NFV, and double PI groups. Average increases over the entire follow-up period were 154, 149 and 169 cells/mm<sup>3</sup>.

#### Disease Progression Summary

Overall, 36 persons experienced a disease progression event or died, 11 on IDV, 15 on NFV, and 11 on assigned the double PI ( $p=0.64$  for difference among groups; Table B4). Six persons assigned IDV died as compared to 13 assigned to NFV and 10 assigned to a double PI ( $p=0.22$ ).

#### Drug Resistance

One hundred and twenty-eight persons had a genotypic resistance test performed in conjunction with their first virologic failure (44 assigned indinavir, 45 assigned nelfinavir, and 39 assigned a double PI). PI mutations were more common on the nelfinavir arm (5 persons versus 1 on each of the other arms) (data not shown).

#### Adverse Events Summary

The rate of grade 4 adverse events was similar among the 3 treatment groups ( $p=0.23$ , Table B4). The most common grade 4 events were elevated liver function tests (4 assigned IDV, 2 assigned NFV, and 4 assigned a double PI) and neutropenia (3 assigned IDV, 1 assigned NFV, and 3 assigned a double PI).

Total cholesterol and triglycerides increased more in the double PI group than in the IDV and NFV groups. LDL and HDL cholesterol levels increased by similar amounts in each of the treatment groups (Table B5).

### Subgroup Analyses

Rate of virologic failure varied according to treatment group and whether the person was assigned to the 2-class or 3-class strategy of FIRST ( $p<0.01$  for interaction; Table B6). Among persons assigned to the 2-class strategy of FIRST (PI + NRTIs), the double PI group had a non-significantly higher rate of virologic failure (70.9 per 100 person years versus about 50 per 100 person years for the IDV and NFV groups). In contrast, for those assigned the 3-class strategy of FIRST (PI + NNRTI + NRTI), the rate of virologic failure was lower on the double PI group (36.5 per 100 person years) than the IDV (89.4) and NFV (59.4) groups ( $p=0.01$  for difference based on logrank test among the 3 groups).

## SUMMARY

The PI substudy of FIRST opened in February 1999 and randomized 167 antiretroviral-naïve HIV-infected persons to initiate therapy with either an indinavir-containing, a nelfinavir-containing, or a double-PI-containing antiretroviral regimen. The three groups did not differ

significantly for the primary virologic outcome or for major secondary outcomes. Power was limited for all outcomes.

**Table B1****Baseline Characteristics by Treatment Group**

<b>Characteristic</b>	<b>Indinavir (N = 58)</b>	<b>Nelfinavir (N = 56)</b>	<b>Double PI (N = 53)</b>	<b>Total (N = 167)</b>
Age (years) (Median, IQR)	37 (31 – 43)	36 (31 – 43.5)	37 (32 – 47)	37 (31 – 44)
Female (%)	17.2	25.0	24.5	22.2
Race/Ethnicity				
Black (%)	67.2	60.7	58.5	62.3
Latino (%)	10.3	19.6	15.1	15.0
White (%)	22.4	17.9	22.6	21.0
Other (%)	0.0	1.8	3.8	1.8
Intravenous drug use (%)	22.4	10.7	18.9	17.4
Hepatitis B (%)	1.9	3.8	12.5	5.9
Hepatitis C (%)	25.9	25.0	18.9	23.4
Prior AIDS (%)	34.5	33.9	35.8	34.7
Baseline <sup>+</sup> CD4 <sup>+</sup> (cells/mm <sup>3</sup> ) (Median, IQR)	184.5 (45.0 – 380.0)	232.3 (20.0 – 448.5)	196.0 (44.0 – 348.0)	197.0 (38.5 – 382.0)
Baseline <sup>+</sup> HIV-RNA (copies/mL) (Median, IQR)	70,827 (22,722-428,184)	173,327 (39,097-419,880)	161,644 (28,474-348,649)	139,917 (30,995-398,822)
Total serum cholesterol (Median, IQR)	164.0 (135.0 – 192.0)	169.5 (146.5 – 208.0)	156.0 (133.0 – 190.0)	163.0 (139.0 – 192.0)
Non-fasting triglycerides (Median, IQR)	134.0 (90.0 – 206.0)	134.0 (94.5– 198.5)	130.0 (82.0 – 176.0)	132.5 (86.0 – 198.0)
2-Class strategy (%)	53.4	44.6	45.3	47.9

+ Average of screening and baseline levels.

**Table B2****Other Antiretroviral Treatment (ART) Prescribed at Time of Randomization**

	<b>Indinavir*</b> <b>(N = 58)</b>		<b>Nelfinavir</b> <b>(N = 56)</b>		<b>Double PI**</b> <b>(N = 53)</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
<b><u>NNRTI</u></b>						
EFV	14	24.1	14	25.0	12	22.6
NVP	12	20.7	17	30.4	16	30.2
No NNRTI	32	55.2	25	44.6	25	47.2
<b><u>NRTI</u></b>						
ZDV + 3TC	12	20.7	13	23.2	8	15.1
d4T + 3TC	7	12.1	2	3.6	4	7.5
ABC + d4T	3	5.2	6	10.7	1	1.9
ABC + 3TC	16	27.6	15	26.8	17	32.1
ddI + d4T	13	22.4	15	26.8	14	26.4
Other 2NRTIs	0	0.0	0	0.0	0	0.0
Single NRTI	4	6.9	4	7.1	7	13.2
3NRTIs	0	0.0	1	1.8	0	0.0
No NRTI	3	5.2	0	0.0	2	3.8
No ART	3	5.2	0	0.0	1	1.9

\* Four patients did not take assigned indinavir.

\*\* One patient took one PI (indinavir only) and one patient did not take any PI.

**Table B3****Adherence to Assigned Treatment**

	<u>Indinavir (N = 58)</u>		<u>Nelfinavir (N = 56)</u>		<u>Double PIs (N = 53)</u>		<u>P-Value</u>
	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	
<b>Overall</b>							
Switched to other PI	16	27.6	10	17.9	15	28.3	0.36
Discontinued assigned PI	33	56.9	36	64.3	31	58.5	0.70
<b>2-Class strategy</b>							
Switched to other PI	10	32.3	5	20.0	6	25.0	0.58
Discontinued assigned PI	16	51.6	14	56.0	15	62.5	0.72
Initiated NNRTI	14	45.2	7	28.0	12	50.0	0.26
While on assigned PI	1	3.2	0	0.0	0	0.0	0.45
Not on assigned PI	13	41.9	7	28.0	12	50.0	0.28
Switched NRTI	21	67.7	18	72.0	21	87.5	0.23
While on assigned PI	1	3.2	0	0.0	3	12.5	0.12
Not on assigned PI	20	64.5	18	72.0	18	75.0	0.68
<b>3-Class strategy</b>							
Switched to other PI	6	22.2	5	16.1	9	31.0	0.39
Discontinued assigned PI	17	63.0	22	71.0	16	55.2	0.45
Discontinued NNRTI	21	77.8	24	77.4	21	72.4	0.87
While on assigned PI	2	7.4	5	16.1	3	10.3	0.57
Not on assigned PI	19	70.4	19	61.3	18	62.1	0.74
Switched NNRTI	1	3.7	2	6.5	0	0.0	0.39
While on assigned PI	0	0.0	2	6.5	0	0.0	0.16
Not on assigned PI	1	3.7	0	0.0	0	0.0	0.33
Switched NRTI	21	77.8	27	87.1	23	79.3	0.61
While on assigned PI	3	11.1	5	16.1	3	10.3	0.77
Not on assigned PI	18	66.7	22	71.0	20	69.0	0.94

**Table B4****Summary of Virologic and Clinical Responses**

<b>Event</b>	<b>Indinavir (N = 58)</b>		<b>Nelfinavir (N = 56)</b>		<b>Double PI (N = 53)</b>		<b>P-Value</b>
	<b>N</b>	<b>Rate</b>	<b>N</b>	<b>Rate</b>	<b>N</b>	<b>Rate</b>	
Viral Load > 50 copies/mL after 8 months	48	65.6	48	56.5	42	47.4	0.58
Viral Load > 50 copies/mL after 8 months or death	52	64.1	50	53.4	45	47.8	0.50
Progression to AIDS or death	11	4.1	15	5.9	11	4.7	0.64
Death	6	2.1	13	4.8	10	4.0	0.22
Grade 4 Event	14	6.0	17	7.6	20	11.2	0.23
Progression to AIDS or death or grade 4 events	20	8.8	24	11.4	26	14.8	0.26

**Table B5**  
**Change in Blood Lipids, Glucose and Insulin by**  
**Treatment Group**  
**(Intent-to-Treat Analyses)**

	<b>Indinavir (N = 58)</b>		<b>Nelfinavir (N = 56)</b>		<b>Double PI (N = 53)</b>		<b>P-Value</b>
	<b>No.</b>	<b>Mean Change</b>	<b>No.</b>	<b>Mean Change</b>	<b>No.</b>	<b>Mean Change</b>	
Total serum cholesterol (mg/dl)	57	16.7	56	15.9	51	27.8	0.35
Non-fasting triglycerides (mg/dl)	57	7.2	56	6.7	51	65.5	< 0.01
<b><u>Fasting Lipids*</u></b>							
Total cholesterol (mg/dl)	23	12.5	19	20.0	26	31.4	0.26
Triglycerides (mg/dl)	23	14.0	19	16.9	26	68.5	0.04
LDL cholesterol (mg/dl)	23	4.0	19	8.8	26	12.1	0.42
HDL cholesterol (mg/dl)	23	5.5	19	8.2	26	6.5	0.92
Glucose (mg/dl)*	23	3.8	19	0.4	26	6.1	0.60
Insulin (mL)*	23	2.3	19	3.8	26	4.0	0.93

\* Metabolic substudy (CPCRA 061) patients only

**Table B5 (continued)**  
**Change in Blood Lipids, Glucose and Insulin by**  
**Treatment Group**  
**(On-Treatment Analyses)**

	<b>Indinavir (N = 58)</b>		<b>Nelfinavir (N = 56)</b>		<b>Double PI (N = 53)</b>		<b>P-Value</b>
	<b>No.</b>	<b>Mean Change</b>	<b>No.</b>	<b>Mean Change</b>	<b>No.</b>	<b>Mean Change</b>	
Total serum cholesterol (mg/dl)	51	20.3	53	26.1	41	42.4	0.04
Non-fasting triglycerides (mg/dl)	51	-0.03	53	18.6	41	96.3	< 0.01
<b><u>Fasting Lipids*</u></b>							
Total cholesterol (mg/dl)	22	19.4	17	30.1	22	37.0	0.03
Triglycerides (mg/dl)	22	4.6	17	16.1	22	84.8	0.40
LDL cholesterol (mg/dl)	22	13.4	17	19.3	22	17.3	0.56
HDL cholesterol (mg/dl)	22	3.9	17	7.9	22	5.9	0.61
Glucose (mg/dl)*	22	4.1	17	-3.3	22	5.9	0.71
Insulin (mL)*	22	-0.2	17	4.5	22	5.2	0.37

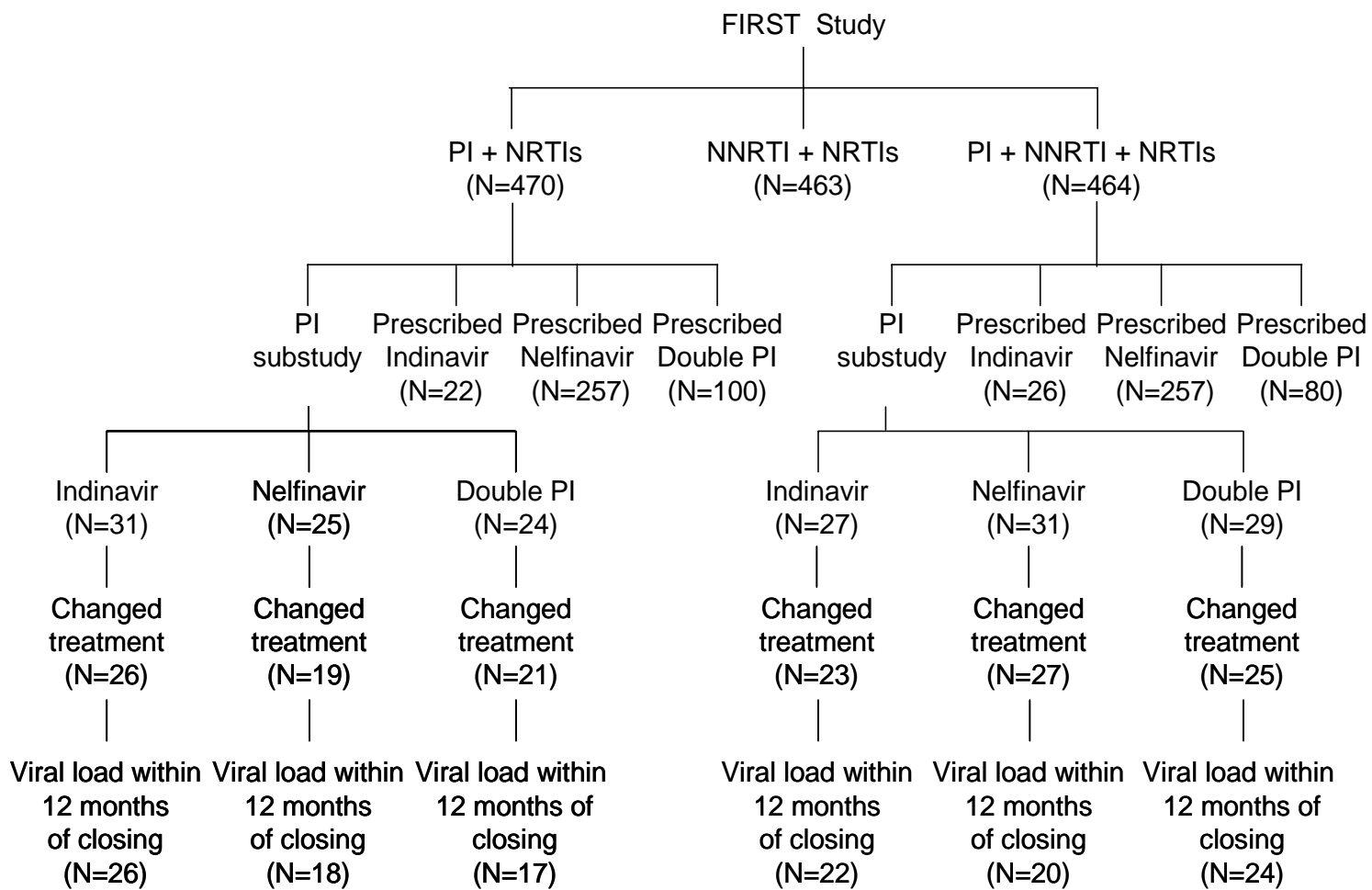
\* Metabolic substudy (CPCRA 061) patients only

**Table B6****Rate of Death or HIV RNA >50 copies/mL  
During Follow-up by Selected Baseline Subgroups**

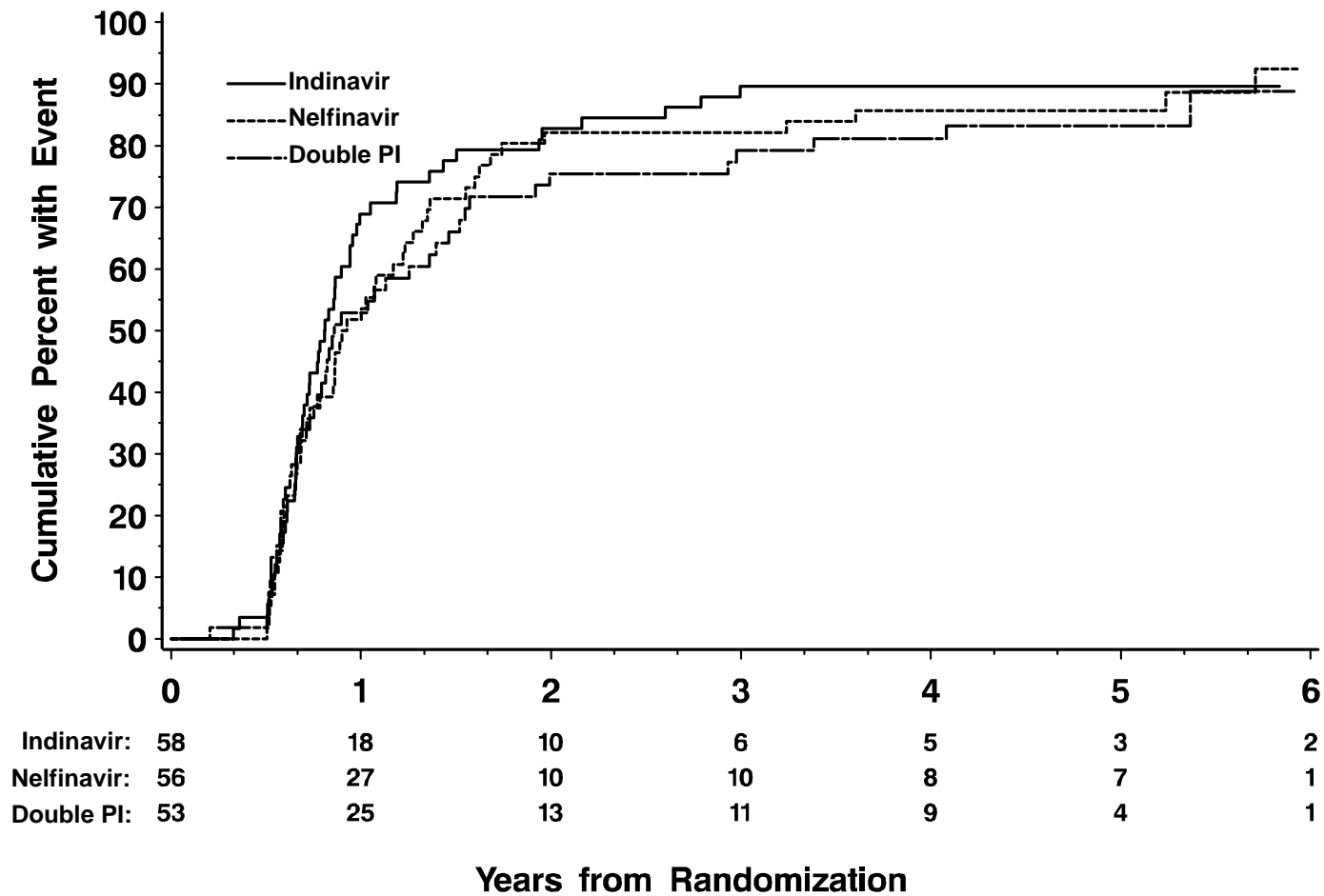
<b>Baseline Subgroup</b>	<b>Indinavir</b>		<b>Nelfinavir</b>		<b>Double PI</b>		<b>P-Value</b>	<b>Interaction P-Value</b>
	<b>N</b>	<b>Rate</b>	<b>N</b>	<b>Rate</b>	<b>N</b>	<b>Rate</b>		
Gender								0.68
Male	48	61.2	42	56.8	40	42.5	0.85	
Female	10	82.2	14	45.1	13	72.0	0.98	
Race								0.12
Latino	6	107.4	11	22.6	8	61.2	0.04	
Black	39	67.2	34	88.4	31	48.0	0.39	
White/Other	13	46.9	11	39.7	14	41.9	0.94	
Randomized to								< 0.01
2-class strategies	31	49.9	25	46.9	24	70.4	0.33	
3-class strategy	27	89.4	31	59.4	29	36.5	0.01	
In NRTI substudy								0.62
Yes	29	72.8	30	52.9	32	49.1	0.53	
No	29	57.2	26	54.1	21	45.9	0.67	

Rates are per 100 person years.

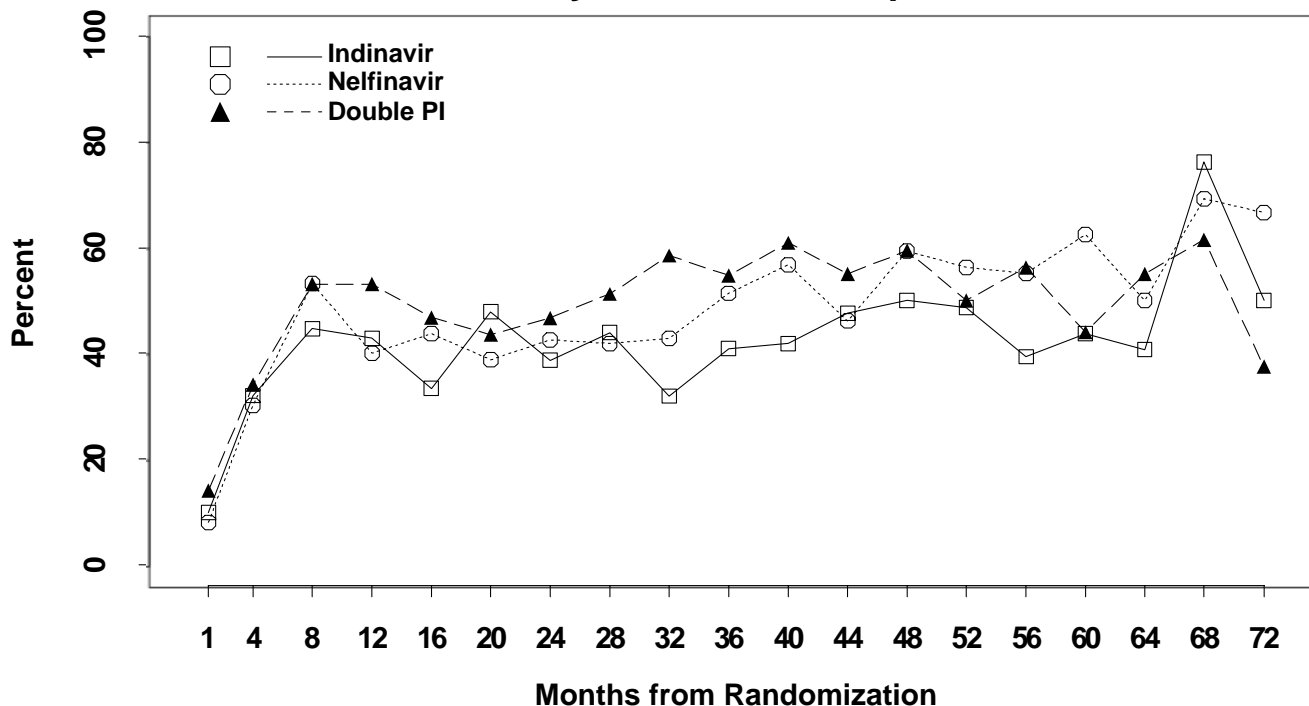
**Figure B1  
PI Substudy**



**Figure B2**  
**Time to Death or First HIV RNA > 50 copies/mL at or after Month 8 Visit**  
**by Treatment Group**



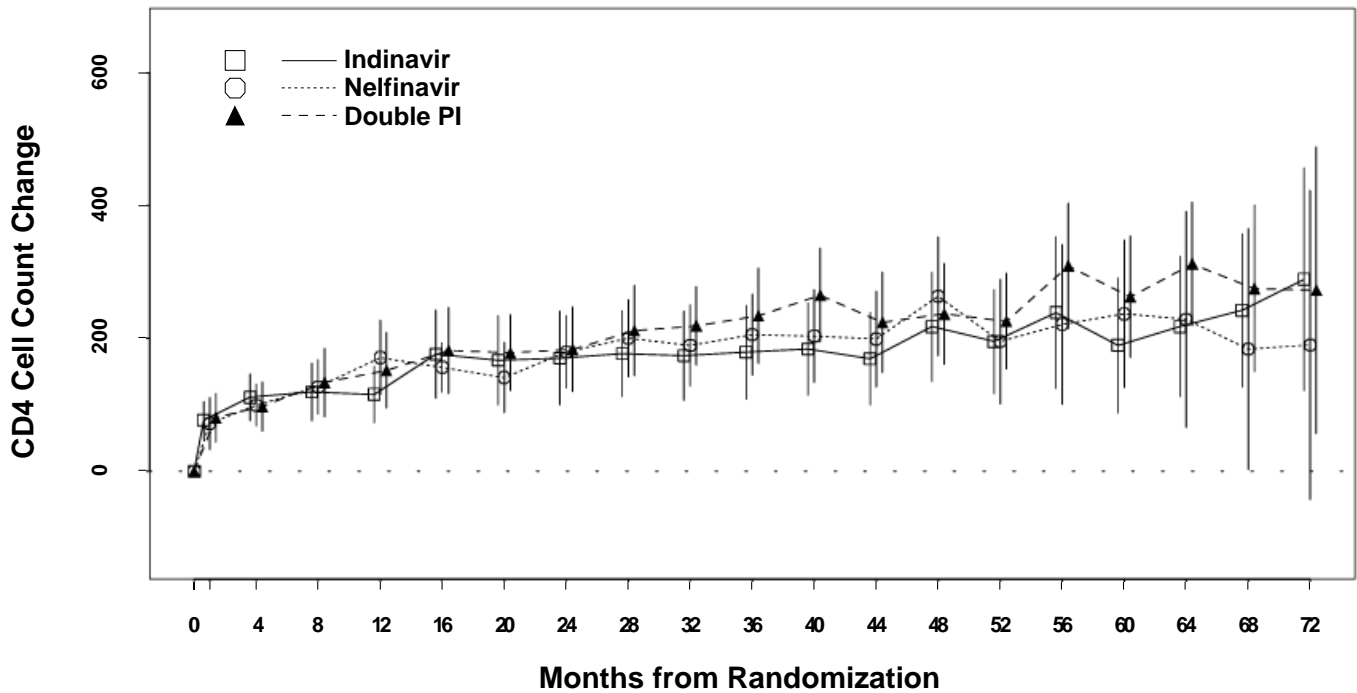
**Figure B3**  
**Percent of Patients with HIV RNA < 50 copies/mL**  
**by Treatment Group**



	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
<b>No. of Patients</b>																				
<b>Indinavir:</b>	51	50	47	49	45	46	44	41	47	44	43	42	42	37	33	32	27	21	14	
<b>Nelfinavir:</b>	50	53	47	50	48	49	47	43	42	37	37	39	32	32	29	24	20	13	9	
<b>Double PI:</b>	50	50	49	49	47	46	45	41	41	42	41	40	37	34	32	25	20	13	8	
<b>p values:</b>	0.61	0.92	0.64	0.39	0.39	0.67	0.75	0.67	0.04	0.41	0.18	0.70	0.63	0.80	0.32	0.31	0.61	0.66	0.48	

\* Percentage is based on the number of patients who have a HIV RNA value at the specific time point

**Figure B4**  
**Mean Change (+- 2SE) from Baseline in CD4+ Cell Count (cells/mm3)**  
**by Treatment Group**



**No. of Patients**

Indinavir:	58	51	50	50	51	46	47	48	47	50	46	45	44	44	39	34	33	29	23	15
Nelfinavir:	56	52	53	48	50	49	49	48	46	43	41	39	41	34	32	30	25	20	13	9
Double PI:	<b>53</b>	50	50	49	49	48	46	45	41	41	43	42	42	39	37	32	26	20	13	8
p values*:	0.95	0.85	0.85	0.33	0.80	0.67	0.97	0.81	0.74	0.62	0.32	0.71	0.76	0.81	0.50	0.62	0.59	0.84	0.90	

\* Adjusted for baseline value