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HIV salvage therapy does not require nucleoside reverse transcriptase inhibitors: a randomized trial

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Abstract

Background—Nucleoside reverse transcriptase inhibitors (NRTIs) are often included in antiretroviral (ARV) regimens in treatment-experienced patients in the absence of data from randomized trials.

Objective—To compare treatment success between participants who omit versus Add NRTIs to an optimized ARV regimen of three or more agents.

Design—Multisite, randomized, controlled trial.

Setting—Outpatient HIV clinics.

Participants—HIV-infected patients with three-class ARV experience and/or viral resistance.

Intervention—Open-label optimized regimens (not including NRTIs) were selected based upon treatment history and susceptibility testing. Participants were randomized to Omit or Add NRTIs.

Measurements—The primary efficacy outcome was regimen failure through week 48, using a non-inferiority margin of 15%. The primary safety outcome was time to initial episode of severe sign/symptom or laboratory abnormality prior to discontinuation of NRTI assignment.

Results—360 participants were randomized and 93% completed a week 48 visit. The cumulative probability of regimen failure was 29.8% in the Omit NRTI arm versus 25.9% in the Add NRTI arm (difference= 3.2%: 95% CI, −6.1 to 12.5). There were no significant differences in the primary safety endpoints or the proportion of participants with HIV RNA <50 copies/mL between arms. No deaths occurred in the Omit NRTIs arm, compared with 7 deaths in the Add NRTIs arm.

Limitations—Non-blinded study design and may not be applicable to resource poor settings.

Conclusion—HIV-infected treatment-experienced patients starting a new optimized regimen can safely omit NRTIs without compromising virologic efficacy. Omitting NRTIs will reduce pill burden, cost, and toxicity in this patient population.

INTRODUCTION

Guidelines for treatment of ARV-experienced HIV-infected patients who are failing therapy recommend using a new regimen that combines at least 2, and preferably 3, fully active medications to suppress viral replication (1-2). Recommendations regarding which agents to use are lacking and fully active medications may not be available due to drug resistance. When starting a new regimen in ARV-experienced patients, the standard of care includes nucleoside/tide reverse transcriptase inhibitors (NRTIs) even though ARV-experienced patients have HIV isolates with mutations that significantly compromise NRTI activity. If NRTIs do not contribute to virologic suppression in a well-constructed regimen, their inclusion will only add to the pill burden, cost, and potential toxicity.

The availability of several newer ARV agents, which act on targets distinct from the NRTIs, has enabled clinicians to construct regimens using drug resistance assays that include more

than two active drugs without using NRTIs. These newer non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs) and entry inhibitors (EIs) can be combined to construct optimized regimens. We hypothesized that, in the setting of a continuous phenotypic susceptibility score (cPSS) of >2 (a research measure of ARV activity), a new regimen that omitted NRTIs would not be inferior to the addition of NRTIs. We designed AIDS Clinical Trials Group (ACTG) A5241 (OPTIONS), a multicenter, randomized, open-label, prospective study, to evaluate treatment success and safety in participants taking a new ARV regimen that omitted or added NRTIs.

METHODS

Design Overview

The OPTIONS trial (ACTG A5241) is an open-label, prospective randomized study evaluating the benefits and risks of omitting versus adding NRTIs to a new optimized ARV regimen (3). The study population consists of HIV-infected individuals failing a PI-based regimen with triple class experience (NNRTIs, NRTIs and PIs) or viral resistance. Participants were randomly assigned to receive an optimized regimen (Omit NRTIs Arm) or to add NRTIs (Add NRTIs Arm) to the optimized regimen. Optimized regimens and NRTI regimens were constructed based upon treatment history, viral resistance and co-receptor tropism tests (performed by Monogram Biosciences -PhenoSense GT® and Trofile®).The planned primary outcome was regimen failure defined as virologic failure or randomized NRTI arm assignment change evaluated through 48 weeks. Two important changes to the study design included: introduction of the enhanced Trofile® assay (Monogram Biosciences, Inc.) on June 13, 2008 that increased the sensitivity to be able to detect non-R5 using virus by using the complete gp160 coding region of the HIV-1 envelope protein with CLIA validation experiments demonstrating success at detecting 0.3% CXCR4-using minor variants; and on April 8, 2009 extending follow up through week 96 to allow for evaluation of the durability of treatment (data not presented). The Institutional Review Board at each participating site approved the study protocol. Written informed consent was obtained from all participants in compliance with human experimentation guidelines (U.S. Department of Health and Human Services).

Study Participants and Eligibility Criteria

Study participants were recruited from 62 outpatient medical clinics into the trial centers across the United States recruited from March 2008 through May 2011 with follow-up through 48 weeks (May 31, 2012). The study population included HIV-1-infected individuals who were at least 16 years of age, with plasma HIV RNA levels ≥1000 copies/mL while taking a PI-containing ARV regimen, who had prior experience or evidence of resistance to NRTI and NNRTI agents, and had acceptable laboratory values including a calculated creatinine clearance ≥50 mL/minute. Persons were ineligible if they had active hepatitis B infection, were pregnant or breastfeeding, or were using prohibited medications. A key criterion for randomization was that an individualized regimen with cPSS>2.0 could be constructed using approved ARV medications excluding NRTIs. A cPSS score (0=not susceptible to 1=susceptible) was calculated (see Supplement Table 1) or

assigned for each drug in a potential regimen based on participant's prior drug exposure, virus susceptibility, and tropism result. The regimen cPSS was then calculated by adding together the cPSS for each drug in the regimen (Note: cPSS is largely a research tool). For complete details on inclusion and exclusion criteria see Supplement Table 2.

Randomization and Intervention

Participants were randomized to Omit or Add NRTIs after choosing an optimized regimen and NRTI regimen. The centralized, computer-based permuted blocked randomization (blocks of 4) was stratified by enfuvirtide (ENF) or INSTI experience (any vs. none), choice of a maraviroc (MVC)-containing regimen (yes/no) and NRTI susceptibility (susceptible to none vs. susceptible to 1 or more NRTIs). NRTI susceptibility for stratification was defined by the 'Net Assessment' among the entire panel of NRTIs tested in the genotype/phenotype resistance test performed at screening. Prior to randomization, a cPSS was calculated for each participant for twenty different optimized regimens. One or more optimized regimens with a cPSS above 2.0 and NRTI regimens were recommended by the study team and sent to sites for selection prior to randomization. Site investigators and study participants selected an optimized regimen and NRTI regimen. Regimen recommendations were influenced by any prior intolerance or allergy to ARVs and the participant's willingness to use ENF. Typically sites received recommendations for between one to six optimized regimens and three to four NRTI combinations in a prioritized order from the study team (the number of options was dependent upon the cPSS of each potential regimen). Twenty possible twice-daily optimized regimens(3-4) consisting of 3-4 medications (not counting ritonavir), taken orally twice daily unless otherwise noted, were composed from the following drugs: 600 mg of darunavir (DRV; Janssen Pharmaceuticals, Inc.) with 100 mg of ritonavir (RTV; Abbvie), 90 mg enfuvirtide by subcutaneous injection (ENF; Roche Pharmaceuticals, Inc.), 200 mg of etravirine (ETR; Janssen Pharmaceuticals, Inc.), 400 mg of raltegravir (RAL; Merck & Co., Inc.), and 500 mg of tipranavir (TPV; Boehringer Ingelheim) with 200 mg of ritonavir; maraviroc (MVC; ViiV Healthcare) was given as 150 mg, 300 mg or 600 mg twice daily – depending on other drugs in the regimen -- according to package insert recommendations (4). Placebos were not used and all drugs were open-label (site investigators and participants were not blinded).

Outcomes and Follow-up

Study evaluations were completed before entry, at entry, at weeks 1, 4, 8, 12, 16, and 24, and every 12 weeks thereafter for the duration of study follow-up in all participants. Treatment adherence was assessed by self-report at every visit by a standardized questionnaire. Adherence counseling was recommended by the study team to include pill/vial counts from returned bottles and vials of ENF. The primary efficacy outcome was regimen failure through 48 weeks, a composite outcome of first confirmed virologic failure (VF), or discontinuation of randomized NRTI assignment. The latter occurred when a participant randomized to the Omit NRTIs Arm started any NRTI or when a participant randomized to the Add NRTIs Arm never initiated NRTIs or permanently discontinued all NRTIs (event time was scheduled week). Virologic failure (event time was scheduled week of initial RNA) was defined when one of the following occurred (and was confirmed with a repeat RNA measurement): $< 1 \log_{10}$ copies/mL decrease from baseline at the week 12 visit,

virologic rebound >200 copies/mL after suppression to <200 copies/mL, lack of suppression to <200 copies/mL by the week 24 visit, or HIV -1 RNA level ≥200 copies/mL at the week 48 visit. All potential regimen failure outcomes underwent review adjudicated by two non-team members who were blinded to treatment assignment and study site. Plasma HIV-1 RNA was measured (UltraSensitive Roche Amplicor HIV-1 Monitor assay) at Johns Hopkins University. The primary safety outcome was time from treatment start to first Grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than baseline, while the participant was receiving the randomly assigned treatment. Adverse events were graded using the Division of AIDS (NIAID, NIH) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 - December 2004. Secondary outcomes reported here include the following: time from randomization to discontinuation of randomized NRTI assignment; time from randomization to confirmed virologic failure; probability of plasma HIV-1 viral load <50 copies/mL at weeks 24 or 48; probability of self-reported non-adherence to ARV regimen (excluding NRTIs) at weeks 24 or 48; change in CD4 cell count from baseline to weeks 48; occurrence of newly acquired HIV drug resistance between treatment dispensation and confirmed virologic failure. Secondary outcomes not reported here include the following: time from treatment start to first ARV modification excluding NRTIs; change in cardiovascular risk score from baseline to weeks 24 and 48; time from treatment dispensation to serious non-AIDS-defining events; change in fasting non-HDL cholesterol from baseline to weeks 24, 48; and week 96 outcomes.

Statistical Analysis

Based on a planned sample size of 177 participants per arm, the study had 80% power to test for non-inferiority of omitting versus adding NRTIs, with a 1-sided significance level of 2.5%, assuming a failure rate of 35% in each arm, and a non-inferiority margin of 15%. The non-inferiority margin of 15% points was chosen to yield a feasible study design together with a clinically significant margin. Analyses were performed with SAS software, version 9 (SAS Institute, Cary, North Carolina).

The cumulative probability of regimen failure by week 48 (primary outcome) was estimated using a stratified Kaplan-Meier estimator, with strata defined by the four unique ENF/INST experience by MVC-containing regimen groups. These estimates were found by weighting the stratum specific estimates (Proc LIFETEST), by treatment group, using inverse variance weights. Confidence intervals were calculated using the log(-log) transformed Greenwood estimated variance. Participants without regimen failure who left the study prior to week 48 were censored at scheduled week of the last observed visit.

If the upper 95% confidence bound of the stratified difference in cumulative probability of regimen failure between Arms (Omit NRTIs – Add NRTIs) at week 48 were less than 15%, then non-inferiority would be concluded. Tests for statistical interactions between baseline characteristics and treatment effect used a stratified logistic regression model (PROC LOGISTIC).

Safety analyses used superiority hypotheses and stratified log-rank tests (PROC LIFETEST). Due to similarity in results whether stratified or not, cumulative incidence (K-

M) plots for time to the various safety outcomes are unadjusted for strata and estimated cumulative probabilities of events by week 48 were not adjusted for strata.

Between arm comparisons for secondary outcome of changes in CD4 cell count to week 48 used a stratified extension to Wilcoxon–Rank Sum test called van Elteren's test (PROC FREQ). The secondary outcome of an HIV-1 RNA level of <50 copies/mL was compared between arms at week 48 with the use of an exact Cochran-Mantel-Haenszel test (PROC MULTTEST)). All participants with outcomes at week 48 (or baseline and week 48 for CD4), were included in these secondary analyses. Those persons in follow-up at week 24 or week 48 who were missing adherence data (and did not report a reason for missed data) were counted as having missed one or more doses of chosen ARV regimen.

Reported P values are two-sided. Secondary outcomes evaluated between weeks 48 and 96 are not presented. Results from 53 non-randomized participants with a cPSS ≤2.0 are not presented.

Study conduct, safety, and efficacy data were reviewed yearly by an independent NIAID Data and Safety Monitoring Board.

RESULTS

Study Participants

Participants were enrolled between March 2008 and May 2011 at 62 centers in the United States with follow up through 48 weeks completed by May 31, 2012. Of 720 potential participants screened for resistance testing, 516 were available for randomization eligibility screening (Figure 1) and, 360 were randomized. Fifty-three participants could not be randomized because of a cPSS ≤ 2.0 but were assigned treatment with an optimized regimen and NRTIs (data not presented). Baseline characteristics were similar between randomized arms (Table 1).The median cPSS (excluding NRTIs) of chosen regimens was 3.0. Median number of active NRTIs was 1.0. The most common ARV regimen was RAL plus RTV-boosted DRV with ETR (56%); in the arm randomized to Add NRTIs, 81% of participants used tenofovir (TDF) plus emtricitabine (FTC) (or lamivudine [3TC]) (Supplement Table 3). Note that randomization to the Add NRTIs arm occurred after selection of the optimized regimen and NRTIs. Three participants did not start study treatment. A total of 337 (94%) participants completed follow-up, and at each of the eight visits over 48 weeks, at least 95% of participants completed a study visit. In the Add NRTIs arm, 90% of participants reported taking NRTIs for at least 42 weeks. In the Omit NRTIs arm 26 (15%) participants reported missing one or more doses of their chosen ARV regimen by 4-day recall versus 25 (15%) from the Add NRTIs arm at week 24. Results were similar at week 48 (26 (16%) in Omit NRTIs arm, and 30 (18%) in Add NRTIs arm).

Primary Outcome of Regimen Failure

There were 53 regimen failures in the Omit NRTIs Arm and 48 in the Add NRTIs Arm (Figure 2). Only 5 participants left the study prior to week 48 and were not adjudicated as regimen failures. The estimated cumulative probabilities of regimen failure by week 48 were 29.8% and 25.9% in the Omit and Add NRTIs Arms, respectively (estimated difference=

3.2%; 95% CI: −6.1, 12.5), allowing for the conclusion of non-inferiority between arms. The time to regimen failure was not different between the Omit versus Add NRTIs arms (stratified log-rank P = 0.50, Supplement Figure 1). Of the 101 regimen failure events, 83 were triggered by virologic failure (41 in the Omit and 42 in the Add NRTIs arm), 16 were triggered by NRTI strategy discontinuation (10 and 6 respectively, see Supplement Table 4) and 2 had both concurrently (Omit NRTIs arm). The separate endpoints of confirmed virologic failure and NRTI strategy discontinuation each demonstrated non-inferiority of the Omit NRTI randomized arm (Figure 2).

When the primary endpoint of regimen failure was examined by sex, race, number of active NRTIs, viral tropism, stratification factors, cPSS of the regimen, or the use of ENF, there was no evidence of significant differences in treatment effect (Supplement Figure 2).

HIV-1 RNA AND CD4 Cell Count Changes Over Time

In the Omit NRTIs Arm, 64% (95% CI: 56%, 72%) of participants with available HIV-1 RNA results had <50 copies/mL at week 48, compared to 66% in the Add NRTIs Arm (95% CI 59% to 73%, Figure 3A; P =0.73). Among those with baseline and week 48 values, the median CD4 increase from baseline to week 48 (Figure 3B) was 90 cells/mm^3 (IQR, 33-167) in the Omit NRTIs arm and 106 cells/mm^3 (IQR, 46-214) in the Add NRTIs arm (P = 0.112).

Adverse Events and Changes in Creatinine and Lipids

The estimated probability of a primary safety event was 38% (95% CI: 32%, 46%; Figure 4A) in the Omit NRTIs arm versus 35% (95% CI: 28%, 43%) in the Add NRTIs arm (P = 0.93). Time to first severe or worse sign or symptom was not significantly different between arms. (P = 0.149; Figure 4B and Supplement Table 5). The Omit NRTIs arm had a non-significantly shorter time to first severe or worse laboratory abnormality compared to the Add NRTIs arm (P = 0.093; Figure 4C), related primarily to lipid elevations. Grade 3 or higher hepatic abnormalities were rare (4% and 2% in the Omit versus Add NRTIs Arm) as were creatinine elevations (2% in each arm). Larger increases in lipid values were seen in the Omit compared to Add NRTIs arm, while creatinine clearance changes were not significantly different between arms (Supplement Table 6).

Serious Adverse Events and Deaths

Thirty-seven (21%) and 44 (24%) participants in the Omit and Add NRTIs Arms experienced a serious adverse event (SAE), respectively. Three SAEs in the Omit and 13 SAEs in the Add NRTIs arms were thought to be at least possibly related to ARV therapy.

Following treatment initiation, there were no deaths in the Omit NRTIs arm and 6 deaths in the Add NRTIs arm (3.3 deaths per 100 person-years; 95% CI: 1.5, 7.4). The causes of death were: 1) heart failure in a participant with lymphoma (week 9 on study treatment), 2) Listeria meningitis (week 17), 3) renal failure (week 21), 4) sepsis with liver failure (week 25), 5) progressive multifocal leukoencephalopathy (week 30), and 6) abdominal bleed in a participant with HCV and cirrhosis (week 52). Three deaths occurred during the pre-randomization screening period (median follow-up of 63 days), when all participants

(n=516) continued on an NRTI-containing regimen, yielding an incidence of death prior to study enrollment of 4.2 per 100 person-years (95% CI: 1.3, 12.9).

Emergence of HIV-1 Drug Resistance among Participants with Virologic Failure

In the Omit NRTI arm, resistance to ETR developed in 9 of 43 (21.0%) participants who underwent resistance testing following virologic failure. In the Add NRTI arm 13 of 45 (29.0%) virologic failure participants developed ETR resistance and 5 of 45 (11.0%) had decreased susceptibility to TDF. Emergence of resistance to other study ARVs was rare.

Of the 177 participants with R5 tropic virus during screening, 70% (124/177) chose a MVC-containing regimen. Twenty-two percent (27/124) of participants on MVC experienced virologic failure, which was similar to the 21% (11/53) virologic failure rate among participants who were eligible, but did not choose a MVC-containing regimen. Among the participants choosing MVC who experienced virologic failure and had viral tropism results, 5/26 (19%) had a shift to dual-mixed virus.

Discussion

The OPTIONS trial was a multicenter, randomized study in treatment-experienced patients failing their current PI-based therapy that included NRTIs, demonstrated that the addition of NRTIs, the cornerstone of initial ARV regimens (1), can be safely omitted if a new optimized regimen contains multiple fully or partially active ARV medications with a cPSS > 2.0. Most participants in this trial chose a regimen with 3-4 ARVs with partial or full activity. Through 48 weeks of follow-up, regimen failure, which combined confirmed virologic failure and discontinuation of the NRTI assignment, was not more likely if NRTIs were omitted from the new optimized regimens. The non-inferiority conclusion was robust and consistent across sensitivity analyses including analysis of the separate components of the primary regimen failure endpoint. No significant differences in regimen failure between arms were observed in subgroups of participants defined by stratification factors, demographics, or initial cPSS <3.0. Furthermore, HIV RNA suppression to <50 copies/mL, CD4 cell count gain, and time to regimen failure were similar in the Omit and Add NRTI arms. Therefore, among treatment-experienced patients starting an ARV regimen with a cPSS >2.0, there is strong and consistent evidence that adding NRTIs is not necessary to achieve optimal outcomes.

This study adds substantially to our knowledge of optimal therapy for treatment-experienced patients. In small and observational studies, NRTI-sparing regimens showed promise for treatment of patients with ARV drug resistance (5-8). In two large, randomized studies conducted in resource-limited settings for virologic failure of a first-line NNRTI regimen, RAL plus lopinavir/ritonavir (LPV/r) was non-inferior to 2 NRTIs plus LPV/r (9-10). Studies evaluating new regimens in treatment-experienced participants with limited options had only few patients taking NRTI-sparing regimens (11-14). For example, in the TRIO study, which evaluated DRV + ETR + RAL in experienced patients, only 16% received a regimen without NRTI (14). Thus, that trial could not answer whether NRTIs should be included in ARV-experienced patients starting several active agents.

There were an unexplained greater number of deaths in the Add NRTIs arm compared to the Omit NRTIs arm. The causes of death were similar to those described in large HIV cohort studies (5-18) and could not be clearly attributed to NRTI toxicities. The small number of events limits our ability to conclude that omitting NRTIs leads to reduced mortality.

There some limitations to this study. The role of adding NRTIs to a regimen when the cPSS is ≤ 2.0 was not analyzed. Adding NRTIs may be helpful in persons with a cPSS <2.0. Also, the minimum number of active ARVs required in an optimized regimen without NRTIs is unknown. These results may not apply to resource poor settings where genotypic/phenotypic testing and tropism assays are not available. Finally, study treatment was not blinded to participants and investigators.

Long-term toxicities of NRTIs include decreases in bone mineral density, nephrotoxicity, and potential increased risk of myocardial infarction (19-21). However, over 48 weeks, we did not observe a significant reduction in adverse events within the omit NRTIs arm.

Conclusions

In ARV-experienced patients, NRTIs can be safely omitted from new active regimens provided the cumulative activity of the regimen exceeds that of two fully active agents as measured by current genotypic/phenotypic testing, tropism assay and accounting for prior treatment history. The potential benefits of omitting NRTIs include reduced pill burden, reduced cost and, likely, a decrease in NRTI-associated toxicity over the long-term. These results have been incorporated in recent ARV guideline recommendations for treatment of ARV-experienced patients (2).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential conflicts of interest:

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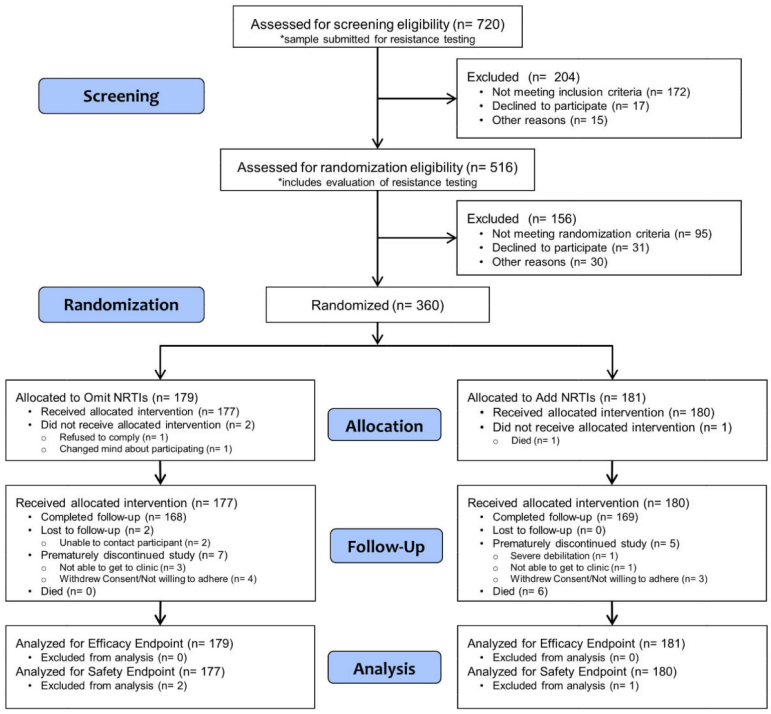

FIGURE 1.

Participant Disposition (CONSORT diagram). The progress of all participants from screening through randomization and analysis are displayed. Key outcomes are identified within each block. Populations for key analyses are also summarized.

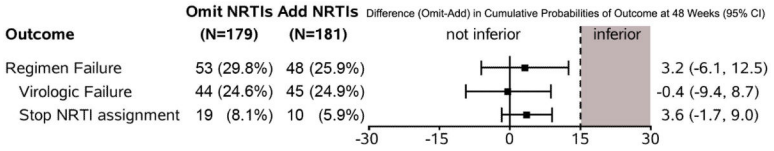

FIGURE 2.

Primary outcome of regimen failure and its individual components (cumulative number of confirmed virologic failures and discontinuations of NRTI assignment). Because a participant may experience both virologic failure and discontinuation of the NRTI assignment, the number of events of the components exceeds the total number of regimen failures. Cumulative probabilities of outcomes by week 48 are given within the parentheses in the table (e.g., 29.8% regimen failure in the Omit NRTI arm). Between arm differences (Omit – Add NRTIs) in the cumulative probabilities with 95% CI are given in the right-most column and are plotted with the black squares and horizontal lines. The non-inferiority margin is denoted by the dashed vertical line. NRTIs = nucleoside reverse transcriptase inhibitors.

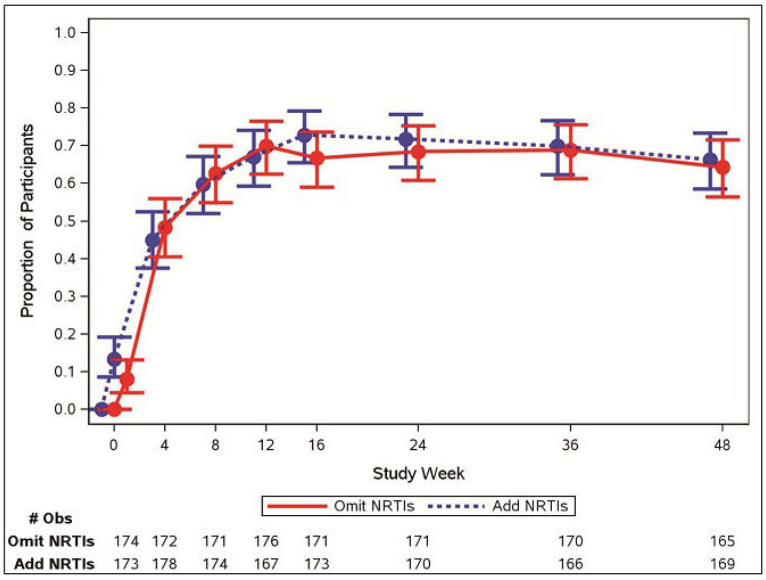

Figure 3A. Proportion of participants with HIV-1 RNA <50 copies

Missing RNA values were excluded. The point estimate (circle) and 95% point-wise CI (vertical lines) are shown. 95% CIs calculated using normal approximation to the binomial. The number of observations in each group for each study week is also presented. All participants in each randomized arm were assessed at Week 0 (Omit NRTIs, N=179; Add NRTIs, N=181).

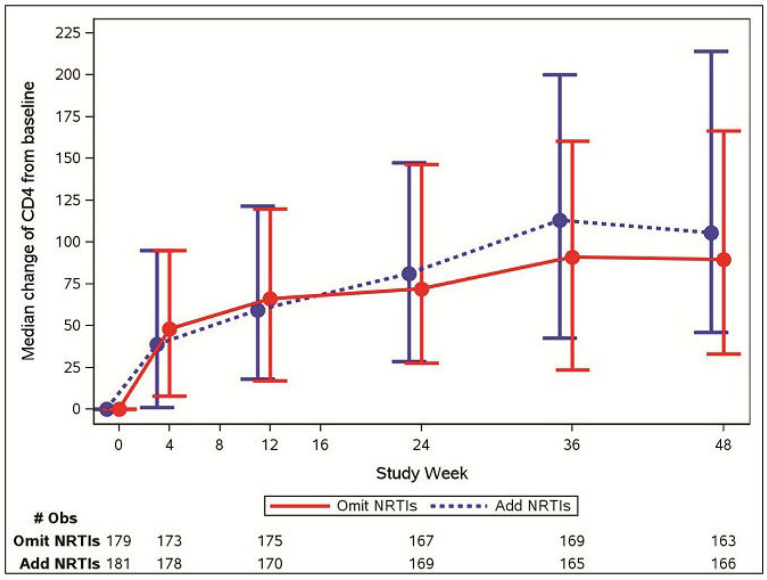

Figure 3B. CD4 cell count changes from baseline for the randomized study arms

The median change (circles) and IQR (lines) are plotted by scheduled study visit. The number of observations in each group for each study week is also presented.

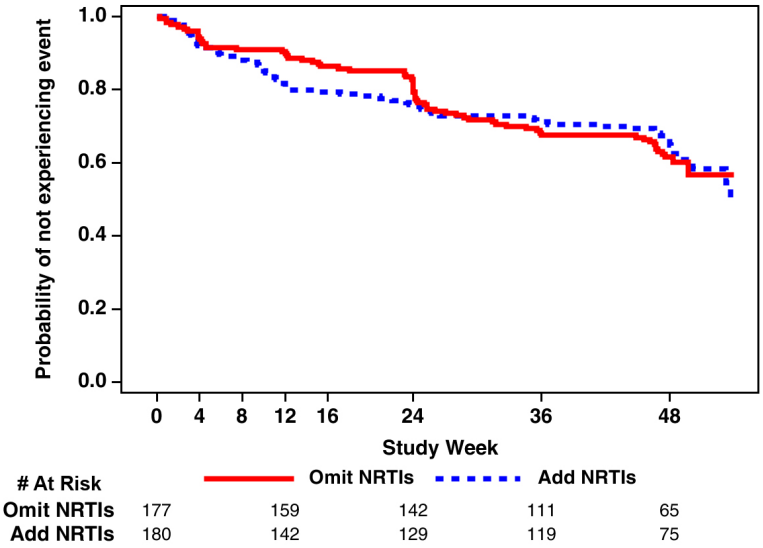

Figure 4A. Primary safety outcome: Time to first Grade 3 or 4 sign or symptom, or laboratory abnormality that was at least one grade above baseline

The results presented are an as-treated analysis (including only those who started study treatment; events occurring after discontinuation of NRTI assignment are censored).

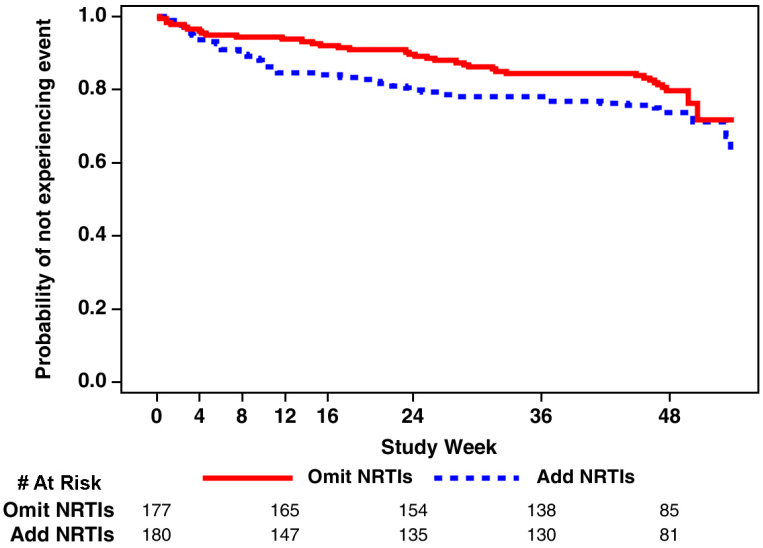

Figure 4B.

Secondary safety outcome: Time to the first Grade 3 or 4 sign or symptom that was at least one grade above baseline. As-treated analysis (including only those who started study treatment, and events occurring after NRTI strategy discontinuation are censored).

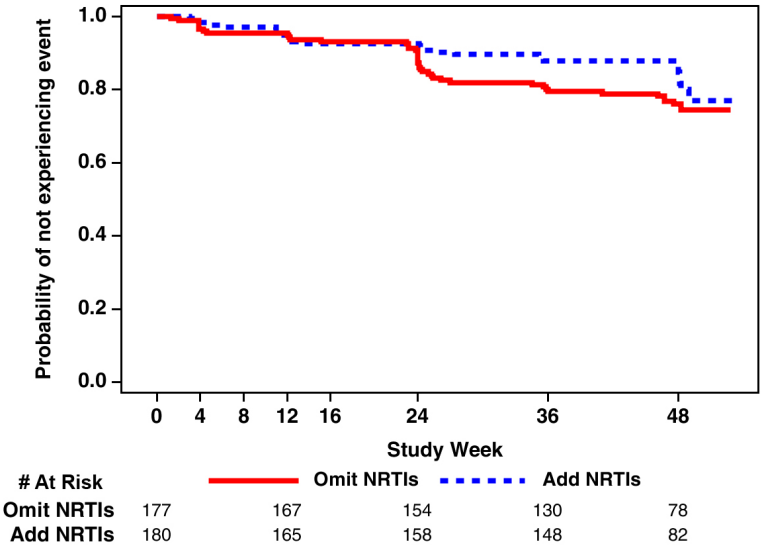

Figure 4C.

Secondary safety outcome: Time to the first Grade 3 or 4 laboratory abnormality that was at least one grade above baseline. As-treated analysis (including only those who started study treatment, and events occurring after NRTI strategy discontinuation are censored).

TABLE 1

Baseline Characteristics of Study Population

Characteristic	Omit NRTIs	Add NRTIs	Total
	N=179	N=181	N=360
Sex: number (%)			
Female	47 (26%)	46 (25%)	93 (26%)
Age: years			
Median (Interquartile range)	46 (40-51)	46 (41-52)	46 (40-52)
Race/ethnicity: number (%)			
White	55 (31%)	59 (33%)	114 (32%)
Black	69 (39%)	79 (44%)	148 (41%)
Hispanic	46 (26%)	37 (21%)	83 (23%)
Other*	8 (4%)	4 (2%)	12 (3%)
HIV-1 RNA (log_{10} copies/mL)			
Median (Interquartile range)	4.2 (3.6-4.6)	4.2 (3.6-4.7)	4.2 (3.6-4.6)
HIV-1 RNA level: number (%)			
< 50,000 copies/mL	148 (83%)	139 (77%)	287 (80%)
≥ 50,000 copies/mL	31 (17%)	42 (23%)	73 (20%)
CD4 count (cells/mm^3)			
Median (Interquartile range)	212 (105-348)	193 (104-376)	207 (105-363)
Hepatitis C: number (%)	19 (11%)	27 (15%)	46 (13%)
Reported history of AIDS: number (%)	80 (45%)	90 (50%)	170 (47%)
Years on ARV: Median (Interquartile range)	12 (9-16)	10.7 (7.5-14)	11.4 (8.3-15)
Years on PIs: Median (Interquartile range)	9.4 (6-11)	8.4 (5-10.8)	9 (5.3-11)
Years on NNRTI: Median (Interquartile range)	1.9 (1.0-3.8)	2 (0.9-3.5)	1.9 (0.9-3.7)
Prior use of enfuvirtide: Number (%)	32 (18%)	29 (16%)	61 (17%)
Prior use of any integrase inhibitor: Number (%)	5 (3%)	4 (2%)	9 (3%)
HIV-1 tropism CCR5 only: Number (%)**	88 (49%)	89 (49%)	177 (49%)
Sensitive to NRTI ***			
Tenofovir	120 (67%)	117 (65%)	237 (66%)
Lamivudine	55 (31%)	52 (29%)	107 (30%)
Emtricitabine	52 (29%)	52 (29%)	104 (29%)
Zidovudine	66 (37%)	78 (43%)	144 (40%)
Abacavir	83 (46%)	92 (51%)	175 (49%)
Sensitive to Etravirine**	161 (90%)	162 (90%)	323 (90%)
Sensitive to specific protease inhibitors**			
Darunavir/ritonavir	135 (75%)	135 (75%)	270 (75%)
Tipranavir/ritonavir	109 (61%)	108 (60%)	217 (60%)
Median regimen cPSS of selected regimen	3	3	3
minimum- maximum	2.4-4	2.3-4	2.3-4
Median active NRTIs of selected NRTI	1	1	1

Characteristic	Omit NRTIs	Add NRTIs	Total
Interquartile range	1-2	1-2	1-2
minimum- maximum	0-3	0-3	0-3

* Race missing for 1 in Omit and 2 in Add NRTIs.

** Overall, 5% CXCR4 only and 6% non- reportable.

*** Sensitive determined by the Monogram “net assessment” which considers both the genotype and phenotype in determining resistance (categorized as sensitive, possible resistance or resistant). Susceptibility reported here is the sensitive category. ARV-Antiretrovirals, PI-Protease inhibitors, NNRTI-Non-nucleoside reverse transcriptase inhibitors, NRTI-Nucleoside/tide reverse transcriptase inhibitors, cPSS-Continuous phenotypic susceptibility score.