ORIGINAL RESEARCH

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HIV Salvage Therapy Does Not Require Nucleoside Reverse Transcriptase Inhibitors

A Randomized, Controlled Trial

Karen T. Tashima, MD; Laura M. Smeaton, MS; Carl J. Fichtenbaum, MD; Adriana Andrade, MD, MPH; Joseph J. Eron, MD; Rajesh T. Gandhi, MD; Victoria A. Johnson, MD; Karin L. Klingman, MD; Justin Ritz, MS; Sally Hodder, MD; Jorge L. Santana, MD; Timothy Wilkin, MD; and Richard H. Haubrich, MD, on behalf of the A5241 Study Team*

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

Objective: To compare treatment success between participants who omit versus those who add NRTIs to an optimized antiretroviral regimen of 3 or more agents.

Design: Multicenter, randomized, controlled trial. (ClinicalTrials.gov: NCT00537394)

Setting: Outpatient HIV clinics.

Participants: Treatment-experienced patients with HIV infection and viral resistance.

Intervention: Open-label optimized regimens (not including NRTIs) were selected on the basis of treatment history and susceptibility testing. Participants were randomly assigned to omit or add NRTIs.

Measurements: The primary efficacy outcome was regimen failure through 48 weeks using a noninferiority margin of 15%. The primary safety outcome was time to initial episode of a severe sign, symptom, or laboratory abnormality before discontinuation of NRTI assignment.

Results: 360 participants were randomly assigned, and 93% completed a 48-week visit. The cumulative probability of regimen failure was 29.8% in the omit-NRTIs group versus 25.9% in the add-NRTIs group (difference, 3.2 percentage points [95% CI, −6.1 to 12.5 percentage points]). No significant between-group differences were found in the primary safety end points or the proportion of participants with HIV RNA level less than 50 copies/mL. No deaths occurred in the omit-NRTIs group compared with 7 deaths in the add-NRTIs group.

Limitation: Unblinded study design, and the study may not be applicable to resource-poor settings.

Conclusion: Treatment-experienced patients with HIV infection 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.

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For author affiliations, see end of text.

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* For members of the A5241 study team, see end of text.

Guidelines for the treatment of HIV-infected patients in whom antiretroviral therapy has failed recommend using a new regimen that combines at least 2, and preferably 3, fully active medications to suppress viral replication (1, 2). Recommendations about which agents to use are lacking, and fully active medications may not be available because of drug resistance. When starting a new regimen in treatment-experienced patients (that is, those who have used antiretroviral drugs before), the standard of care includes nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs); however, treatment-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.

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The availability of several newer antiretroviral agents, which act on targets distinct from the NRTIs, has enabled clinicians to construct regimens using drug resistance assays that include more than 2 active drugs without using NRTIs. These newer non-NRTIs (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors, and entry inhibitors can be combined to construct optimized regimens. We hypothesized that, in the setting of a continuous phenotypic susceptibility score (cPSS) greater than 2 (a research measure of antiretroviral activity), a new regimen that omitted NRTIs would not be inferior to one that added NRTIs. We designed the OPTIONS (Optimized Treatment That Includes or Omits NRTIs) trial to evaluate treatment success and safety in participants receiving a new antiretroviral regimen that omitted or added NRTIs.

METHODS

Design Overview

The OPTIONS trial is a multicenter, open-label, prospective, randomized, controlled study evaluating the benefits and risks of omitting versus adding NRTIs to a new optimized antiretroviral regimen (3). The study population consists of HIV-infected patients for whom a

PI-based regimen has failed and who have triple-class experience (NNRTIs, NRTIs, and PIs) and viral resistance. Participants were randomly assigned to receive an optimized regimen (the omit-NRTIs group) or to add NRTIs to the optimized regimen (the add-NRTIs group). Optimized and NRTI regimens were constructed on the basis of treatment history, viral resistance, and coreceptor tropism tests (performed by Monogram Biosciences using PhenoSense GT and Trofile). The planned primary outcome was regimen failure, defined as virologic failure or change in NRTI group assignment, evaluated through 48 weeks. The study design had 2 important changes. On 13 June 2008, the enhanced Trofile assay (Monogram Biosciences) was introduced and increased the sensitivity in detecting non–R5-using virus by using the complete gp160 coding region of the HIV-1 envelope protein, with clinical laboratory improvement amendment validation experiments showing success at detecting 0.3% CXCR4-using minor variants. On 8 April 2009, follow-up was extended through 96 weeks to evaluate treatment durability (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 from March 2008 through May 2011, with follow-up through 48 weeks (31 May 2012). The study population included HIV-1–infected persons who were at least 16 years of age; had a plasma HIV RNA level of 1000 copies/mL or more; had received a PI-based antiretroviral regimen; had previously used or had evidence of resistance to NRTIs and NNRTIs; and had acceptable laboratory values, including a calculated creatinine clearance of 50 mL/min/1.73 m^2. 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 a cPSS greater than 2.0 could be constructed using study antiretroviral medications, excluding NRTIs. A cPSS (0 [not susceptible] to 1 [susceptible]) was calculated (**Appendix Table 1**, available at www.annals.org) or assigned for each drug in a potential regimen based on the participant's prior drug exposure, virus susceptibility, and tropism result. The regimen cPSS was then calculated by adding together the cPSSs for each drug in the regimen (note that cPSS is largely a research tool). For complete details on inclusion and exclusion criteria, see **Appendix Table 2** (available at www.annals.org).

Randomization and Intervention

Participants were randomly assigned either to omit or to add NRTIs after choosing an optimized regimen and an NRTI regimen. The centralized, computer-based, permuted block randomization (blocks of 4) was stratified by enfuvirtide (ENF) or integrase strand transfer inhibitor use (any vs. none), choice of a maraviroc (MVC)–based regimen (yes vs. no), and NRTI susceptibility (susceptible to 0 vs. ≥1 NRTIs). The NRTI susceptibility criterion was defined by the "net assessment" among the entire panel of NRTIs in the genotype and phenotype resistance test at screening. Before randomization, a cPSS was calculated for each participant for 20 different optimized regimens. One or more optimized regimens with a cPSS greater than 2.0 and NRTI regimens were recommended by the study team and sent to sites for selection before randomization. Site investigators and study participants selected both an optimized regimen and an NRTI combination. Regimen recommendations were influenced by any prior intolerance or allergy to antiretroviral drugs and the participant's willingness to use ENF. Typically, sites received recommendations for between 1 to 6 optimized regimens and 3 to 4 NRTI combinations in a prioritized order from the study team (the number of options was dependent on the cPSS of each potential regimen). Twenty possible optimized regimens (3, 4) consisting of 3 to 4 medications (excluding ritonavir [RTV]) taken orally twice daily, unless otherwise noted, were composed from the following drugs: 600 mg of darunavir with 100 mg of RTV, 90 mg of ENF by subcutaneous injection, 200 mg of etravirine (ETR), 400 mg of raltegravir (RAL), and 500 mg of tipranavir with 200 mg of RTV. Further, 150, 300, or 600 mg of MVC was administered 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).

EDITORS' NOTES

Context

Nucleoside reverse transcriptase inhibitors (NRTIs) are often included in antiretroviral regimens for treatment-experienced patients with HIV infection, but no randomized, controlled trials have evaluated this approach.

Contribution

This large randomized, controlled trial in treatment-experienced patients with HIV infection found no difference in either efficacy or safety when NRTIs were included or excluded in initial optimized antiretroviral regimens. More deaths occurred in the group that added NRTIs to the regimen, but these were not believed to be related to treatment.

Caution

The trial was not blinded.

Implication

Regimens for treatment-experienced patients with HIV infection may not need NRTIs, which could have benefit in terms of cost, toxicity, and pill burden.

Table. Baseline Characteristics of Study Population

Characteristic	Omit-NRTIs Group (*n* = 179)	Add-NRTIs Group (*n* = 181)	Total (*n* = 360)
Women, *n (%)*	47 (26)	46 (25)	93 (26)
Median age (IQR), *y*	46 (40–51)	46 (41–52)	46 (40–52)
Race/ethnicity, *n (%)**			
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)
Median HIV-1 RNA level (IQR), *$\log_{10}$ copies/mL*	4.2 (3.6–4.6)	4.2 (3.6–4.7)	4.2 (3.6–4.6)
HIV-1 RNA level, *n (%)*			
<50 000 copies/mL	148 (83)	139 (77)	287 (80)
≥50 000 copies/mL	31 (17)	42 (23)	73 (20)
Median $CD4^+$ cell count (IQR), *× 10^9 cells/L*	0.212 (0.105–0.348)	0.193 (0.104–0.376)	0.207 (0.105–0.363)
Hepatitis C virus, *n (%)*	19 (11)	27 (15)	46 (13)
Reported history of AIDS, *n (%)*	80 (45)	90 (50)	170 (47)
Median years receiving ART (IQR)	12.0 (9.0–16.0)	10.7 (7.5–14.0)	11.4 (8.3–15.0)
Median years receiving PIs (IQR)	9.4 (6.0–11.0)	8.4 (5.0–10.8)	9.0 (5.3–11.0)
Median years receiving NNRTIs (IQR)	1.9 (1.0–3.8)	2.0 (0.9–3.5)	1.9 (0.9–3.7)
Prior use of ENF, *n (%)*	32 (18)	29 (16)	61 (17)
Prior use of any INSTI, *n (%)*	5 (3)	4 (2)	9 (3)
HIV-1 tropism CCR5 only, *n (%)*†	88 (49)	89 (49)	177 (49)
Sensitive to NRTIs, *n (%)*‡			
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 ETR, *n (%)*‡	161 (90)	162 (90)	323 (90)
Sensitive to specific PIs, *n (%)*‡			
DRV–RTV	135 (75)	135 (75)	270 (75)
TPV–RTV	109 (61)	108 (60)	217 (60)
Median cPSS of selected regimen (minimum, maximum)	3.0 (2.4, 4.0)	3.0 (2.3, 4.0)	3.0 (2.3, 4.0)
Median active NRTIs of selected NRTI (minimum, maximum [IQR]), *n*	1 (1, 2 [0–3])	1 (1, 2 [0–3])	1 (1, 2 [0–3])

ART = antiretroviral therapy; cPSS = continuous phenotypic susceptibility score; DRV = darunavir; ENF = enfuvirtide; ETR = etravirine; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TPV = tipranavir.
* Race missing for 1 participant in whom NRTIs were omitted and 2 in whom NRTIs were added.
† Overall, 40% dual or mixed, CXCR4 only and 6% nonreportable.
‡ Determined by the monogram "net assessment," which considers the genotype and phenotype in determining resistance (categorized as sensitive, possible resistance, or resistant). Susceptibility reported here is the sensitive category.

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 during study follow-up in all participants. Treatment adherence was assessed by self-report at every visit using a standardized questionnaire. Adherence counseling was recommended by the study team to include pill and 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, or discontinuation of NRTI assignment. The latter occurred when a participant in the omit-NRTIs group started any NRTI or when a participant in the add-NRTIs group never initiated NRTIs or permanently discontinued all NRTIs (event time was the scheduled week during which the event was noted). Virologic failure (event time was the scheduled week of initial RNA measurement) was defined when 1 of the following occurred (and was confirmed with another RNA measurement): less than 1–$\log_{10}$ copies/mL decrease from baseline at the 12-week visit, virologic rebound greater than 200 copies/mL after suppression to less than 200 copies/mL, lack of suppression to less than 200 copies/mL by the 24-week visit, or an HIV-1 RNA level of 200 copies/mL or more at the 48-week visit. All potential regimen failure outcomes were reviewed by 2 nonteam members who were blinded to treatment assignment and study site. Plasma HIV-1 RNA was measured (UltraSensitive Cobas Amplicor HIV-1 Monitor UltraSensitive assay, version 1.5, Roche Molecular Systems) at Johns Hopkins University (Baltimore, Maryland). The primary safety outcome was time from treatment dispensation to first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least 1 grade higher than baseline while the participant was receiving treatment. Adverse events were graded using the **Table** for Grading the Severity of Adult and Pediatric Adverse Events (version 1.0, December 2004; National Institute of Allergy and Infectious Diseases Division of AIDS). Secondary outcomes reported here include the time from randomization to discontinuation of NRTI assignment, time from randomization to confirmed virologic failure, probability of a plasma HIV-1 viral load less than 50 copies/mL at 24 or 48 weeks, probability of self-reported nonadherence to antiretroviral regimen (excluding NRTIs) at 24 or 48 weeks, change in $CD4^+$ cell count from baseline to 48 weeks, and occurrence of newly acquired HIV

drug resistance between treatment dispensation and confirmed virologic failure. Secondary outcomes not reported here include the time from treatment dispensation to first antiretroviral modification, excluding NRTIs; change in cardiovascular risk score from baseline to 24 and 48 weeks; time from treatment dispensation to serious non–AIDS-defining events; change in fasting non–high-density lipoprotein cholesterol level from baseline to 24 and 48 weeks; and 96-week outcomes.

Statistical Analysis

On the basis of a planned sample size of 177 participants per group, the study had 80% power to test for the noninferiority of omitting versus adding NRTIs, with a 1-sided significance level of 2.5%, assuming a failure rate of 35% in each group, and a noninferiority margin of 15%. This noninferiority margin was chosen to yield a feasible study design with a clinically significant margin. Analyses were done with SAS, version 9 (SAS Institute).

The cumulative probability of regimen failure by 48 weeks (primary outcome) was estimated using a stratified Kaplan–Meier estimator, with strata defined by the 4 unique groups of ENF or integrase strand transfer inhibitors experience with MVC or non-MVC regimens. These estimates were found by weighting the stratum-specific estimates (PROC LIFETEST), according to treatment group, using inverse variance weights. The CIs were calculated using the log(–log)-transformed Greenwood-estimated variance. Participants without regimen failure who left the study before 48 weeks were censored at the scheduled week of the last visit.

If the upper 95% confidence bound of the stratified difference in cumulative probability of regimen failure between groups at 48 weeks was less than 15%, then noninferiority 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). Because of the similarity in results regardless of stratification, we did not adjust cumulative incidence (Kaplan–Meier) plots of time to the various safety outcomes and estimated cumulative probabilities of events by 48 weeks for strata.

Between-group comparisons of changes in $CD4^+$ cell count by 48 weeks used a stratified extension to the Wilcoxon rank-sum test called the van Elteren test (PROC FREQ). The secondary outcome of an HIV-1 RNA level less than 50 copies/mL was compared between groups at 48 weeks with the use of an exact Cochran–Mantel–Haenszel test (PROC MULTTEST). All participants with outcomes at 48 weeks (or baseline and 48-week outcomes for $CD4^+$ cell count) were included in these secondary analyses. Those in 24- or 48-week follow-up who were missing adherence data (and did not report a reason for missed data) were counted as having missed 1 or more doses of the chosen antiretroviral regimen.

Reported *P* values are 2-sided. Secondary outcomes evaluated between 48 and 96 weeks are not presented. Results from 53 participants who were not randomly assigned and whose available regimens had a cPSS of 2.0 or less are not presented.

Study conduct, safety, and efficacy data were reviewed yearly by an independent National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board.

Role of the Funding Source

The study was supported by the National Institute of Allergy and Infectious Diseases. Study medications were provided by Roche (ENF), ViiV Healthcare (MVC), AbbVie (RTV), Janssen (darunavir and ETR), Merck (RAL), and Boehringer Ingelheim (tipranavir). Monogram Biosciences performed the viral resistance and tropism testing. The funding sources did not have a role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

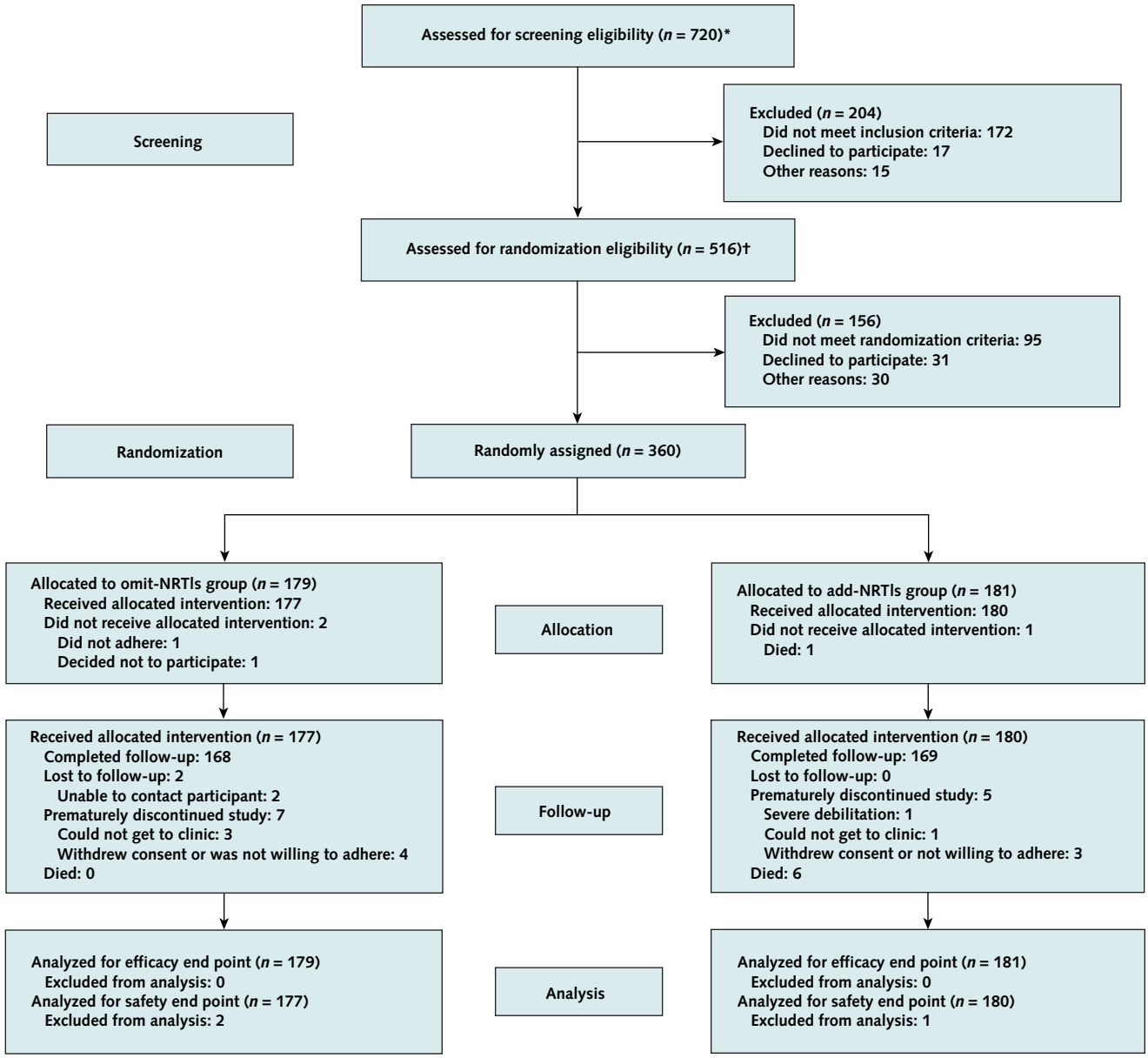
Study Participants

Participants were enrolled between March 2008 and May 2011 at 62 centers in the United States, with follow-up through 48 weeks completed by 31 May 2012. Of 720 potential participants screened for resistance testing, 516 were available for eligibility screening (**Figure 1**); 360 were randomly assigned. Fifty-three participants could not be randomly assigned because only regimens with a cPSS of 2.0 or less could be constructed for them; they were assigned treatment with an optimized regimen and NRTIs (data not presented). Baseline characteristics were similar among the randomized groups (**Table**).The median cPSS of chosen regimens (excluding NRTIs) was 3.0. The median number of active NRTIs was 1.0. The most common antiretroviral regimen was RAL plus RTV-boosted darunavir with ETR (56%); in the add-NRTIs group, 81% of participants used tenofovir plus emtricitabine (or lamivudine) (**Appendix Table 3**, available at www.annals.org). Note that randomization to the add-NRTIs group occurred after selection of the optimized regimen and NRTIs. Three participants did not start the study treatment. A total of 337 (94%) participants completed follow-up, and at each of the 8 visits over 48 weeks, at least 95% of participants completed a study visit. In the add-NRTIs group, 90% of participants reported receiving NRTIs for at least 42 weeks. In the omit-NRTIs group, 26 (15%) participants reported missing 1 or more doses of their chosen antiretroviral regimen by 4-day recall versus 25 (15%) from the add-NRTIs group at 24 weeks. Results were similar at 48 weeks (26 participants [16%] in the omit-NRTIs group and 30 [18%] in add-NRTIs group).

Primary Outcome of Regimen Failure

We noted 53 regimen failures in the omit-NRTIs group and 48 in the add-NRTIs group (**Figure 2**). Only 5

Figure 1. Study flow diagram.



The progress of all participants from screening through randomization and analysis are displayed. Key outcomes are identified, and populations for key analyses are also summarized.
* Sample submitted for resistance testing.
† Includes evaluation of resistance testing.

participants left the study before 48 weeks and were not adjudicated as regimen failures. The estimated cumulative probabilities of regimen failure by 48 weeks were 29.8% and 25.9% in the omit- and add-NRTIs groups, respectively (estimated difference, 3.2 percentage points [95% CI, −6.1 to 12.5 percentage points]), which allowed for the conclusion of noninferiority between the groups. The time to regimen failure did not differ between the groups (stratified log-rank $P = 0.50$) (**Figure 3**, *A*). Of the 101 regimen failures, 83 were triggered by virologic failure (41 and 42 in the omit- and add-NRTIs groups, respectively), 16 were triggered by NRTI strategy discontinuation (10 and 6, respectively) (**Appendix Table 4**, available at www.annals.org), and 2 had both concurrently (omit-NRTIs group). The separate end points of confirmed virologic failure and NRTI strategy discontinuation showed noninferiority of the omit-NRTIs group (**Figure 2**).

When we examined the primary end point of regimen failure by sex, race, number of active NRTIs, viral tropism, stratification factors, cPSS of the regimen, or the use of ENF, we found no evidence of significant differences in treatment effect (**Appendix Figure**, available at www.annals.org).

HIV-1 RNA Level and CD4$^+$ Cell Count Changes Over Time

In the omit-NRTIs group, 64% (CI, 56% to 72%) of participants with available HIV-1 RNA results had less than 50 copies/mL at 48 weeks compared with 66% (CI, 59% to 73%) in the add-NRTIs group (P = 0.73) (**Figure 4**, *top*). Among participants with baseline and 48-week values, the median increase in CD4$^+$ count from baseline to 48 weeks (**Figure 4**, *bottom*) was 0.090 × 10^9 cells/L (interquartile range, 0.033 to 0.167 × 10^9 cells/L) in the omit-NRTIs group and 0.106 × 10^9 cells/L (interquartile range, 0.046 to 0.214 × 10^9 cells/L) in the add-NRTIs group (P = 0.112).

Adverse Events and Changes in Creatinine Clearance and Lipid Levels

The estimated probability of a primary safety event was 38% (CI, 32% to 46%) (**Figure 3**, *B*) in the omit-NRTIs group versus 35% (CI, 28% to 43%) in the add-NRTIs group (P = 0.93). Time to first severe or worse sign or symptom did not significantly differ between groups (P = 0.149) (**Figure 3**, *C*) (**Appendix Table 5**, available at www.annals.org). The omit-NRTIs group had a nonsignificantly shorter time to first severe or worse laboratory abnormality than the add-NRTIs group (P = 0.093) (**Figure 3**, *D*); this was primarily due to lipid elevations. Grade 3 or higher hepatic abnormalities were rare (4% and 2% in the omit- and add-NRTIs groups, respectively) as were elevations in creatinine clearance (2% in each group). The omit-NRTIs group had larger increases in lipid values than the add-NRTIs group, although changes in creatinine clearance did not significantly differ between groups (**Appendix Table 6**, available at www.annals.org).

Serious Adverse Events and Deaths

Thirty-seven (21%) and 44 (24%) participants in the omit- and add-NRTIs groups, respectively, had a serious adverse event. Three serious adverse events in the omit-NRTIs group and 13 in the add-NRTIs group were thought to be at least possibly related to antiretroviral therapy.

After treatment initiation, there were no deaths in the omit-NRTIs group and 6 deaths in the add-NRTIs group (3.3 deaths per 100 person-years [CI, 1.5 to 7.4 deaths per 100 person-years]). The causes of death were as follows: heart failure in a participant with lymphoma (9 weeks on study treatment), *Listeria* meningitis (17 weeks), renal failure (21 weeks), sepsis with liver failure (25 weeks), progressive multifocal leukoencephalopathy (30 weeks), and abdominal bleeding in a participant with hepatitis C virus and cirrhosis (52 weeks). Three deaths occurred during the prerandomization screening period (median follow-up, 63 days), when all participants (n = 516) continued an NRTI-based regimen, yielding an incidence of death before randomization of 4.2 deaths per 100 person-years (CI, 1.3 to 12.9 deaths per 100 person-years).

Emergence of HIV-1 Drug Resistance Among Participants With Virologic Failure

In the omit-NRTIs group, resistance to ETR developed in 9 of 43 (21.0%) participants who had resistance testing after virologic failure. In the add-NRTIs group, 13 of 45 (29.0%) participants with virologic failure developed ETR resistance and 5 of 45 (11.0%) had decreased susceptibility to tenofovir. Emergence of resistance to other study antiretroviral drugs was rare.

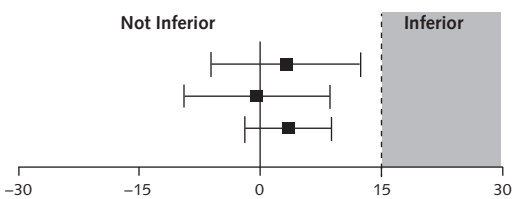
Of the 177 participants with R5 tropic virus found during screening, 70% (124 of 177) chose an MVC-containing regimen. Twenty-two percent (27 of 124) of participants receiving MVC had virologic failure, which was similar to the 21% (11 of 53) rate of virologic failure among participants who were eligible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

DISCUSSION

OPTIONS was a multicenter, randomized, controlled trial in patients for whom current PI-based therapy that included NRTIs had failed. This trial showed that the addition of NRTIs, the cornerstone of initial antiretroviral regimens (1), can be safely omitted if a new optimized regimen contains several fully or partially active antiretroviral medications and the regimen has a cPSS greater than 2.0. Most participants in this trial chose a regimen with 3 to 4 antiretroviral drugs with partial or full activity. Through 48-week follow-up, reg-

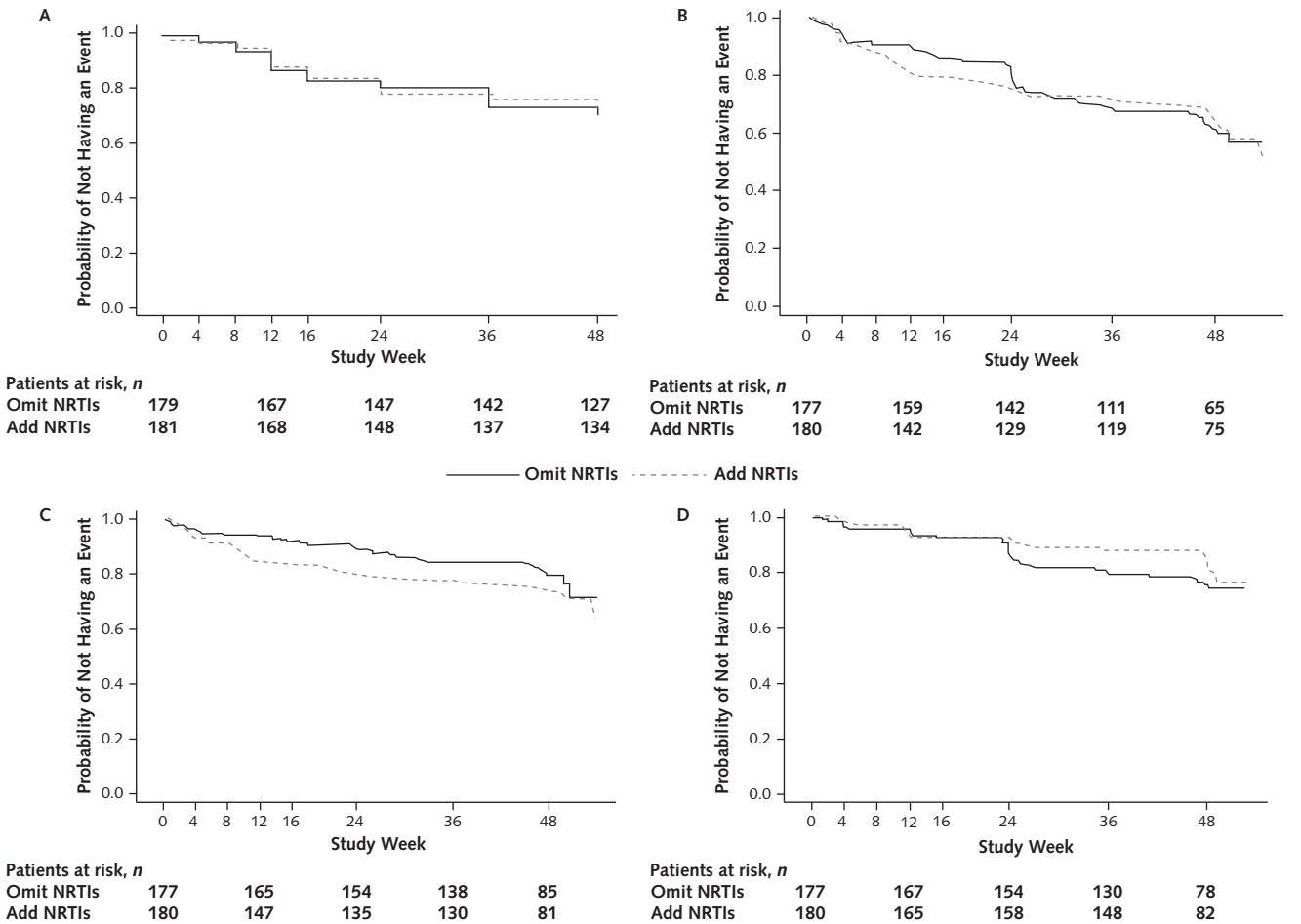
Figure 2. Primary outcome of regimen failure and its subcomponents.

Outcome	Patients, *n* (%)		Difference (95% CI), *percentage points*
	Omit NRTIs (*n* = 179)	Add NRTIs (*n* = 181)	
Regimen failure	53 (29.8)	48 (25.9)	3.2 (–6.1 to 12.5)
Virologic failure	44 (24.6)	45 (24.9)	–0.4 (–9.4 to 8.7)
Stop NRTI assignment	19 (8.1)	10 (5.9)	3.6 (–1.7 to 9.0)



Because a participant may experience virologic failure and discontinue the NRTI regimen assigned, the sum of these events exceeds the total number of regimen failures. Cumulative probabilities of outcomes by 48 wk are given (e.g., 29.8% regimen failure in the omit-NRTIs group). Between-group differences in cumulative probabilities (*squares*) with 95% CIs (*horizontal lines*) are displayed. The noninferiority margin is denoted (*dashed vertical line*). NRTI = nucleoside or nucleotide reverse transcriptase inhibitor.

Figure 3. Time to regimen failure.



Results in panel A are from an intention-to-treat analysis (all randomly assigned participants included). Results in panels B, C, and D are from an as-treated analysis (only participants who started study treatment; events occurring after discontinuation of NRTI assignment are censored). NRTI = nucleoside or nucleotide reverse transcriptase inhibitor. **A.** Secondary efficacy outcome: Time to primary outcome of regimen failure (first virologic failure or discontinuation of NRTI strategy). **B.** Primary safety outcome: Time to first grade 3 or 4 sign, symptom, or laboratory abnormality ≥1 grade higher than baseline. **C.** Secondary safety outcome: Time to first grade 3 or 4 sign or symptom ≥1 grade higher than baseline. **D.** Secondary safety outcome: Time to first grade 3 or 4 laboratory abnormality ≥1 grade higher than baseline.

imen 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 noninferiority conclusion was robust and consistent across sensitivity analyses, including analysis of the separate components of the primary endpoint for regimen failure. No significant differences in regimen failure between groups were seen in subgroups of participants defined by stratification factors, demographics, or an initial cPSS less than 3.0. Further, HIV RNA suppression to less than 50 copies/mL, increase in $CD4^+$ cell count, and time to regimen failure were similar in the omit- and add-NRTIs groups. Therefore, among treatment-experienced patients starting an antiretroviral regimen with a cPSS greater than 2.0, there is strong and consistent evidence that adding NRTIs is not necessary to achieve optimal outcomes.

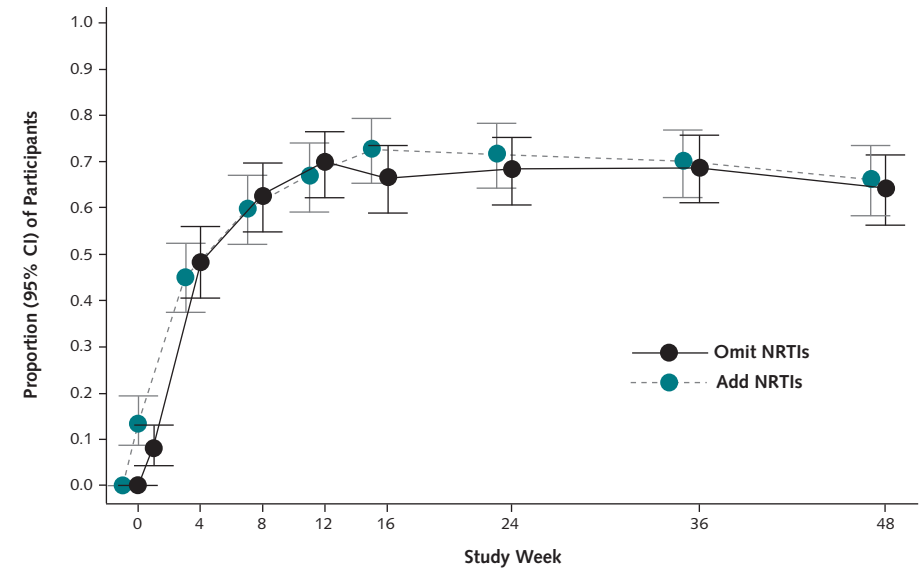
This study adds substantially to our knowledge of optimal therapy for treatment-experienced patients. In small and observational studies, NRTI-sparing regimens showed promise for treatment of patients with antiretroviral drug resistance (5–8). In 2 large randomized studies conducted in resource-limited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

We noticed more unexplained deaths in the add-NRTIs group than in the omit-NRTIs group. The causes of death were similar to those described in large HIV cohort studies (15–18) and could not be clearly attrib-

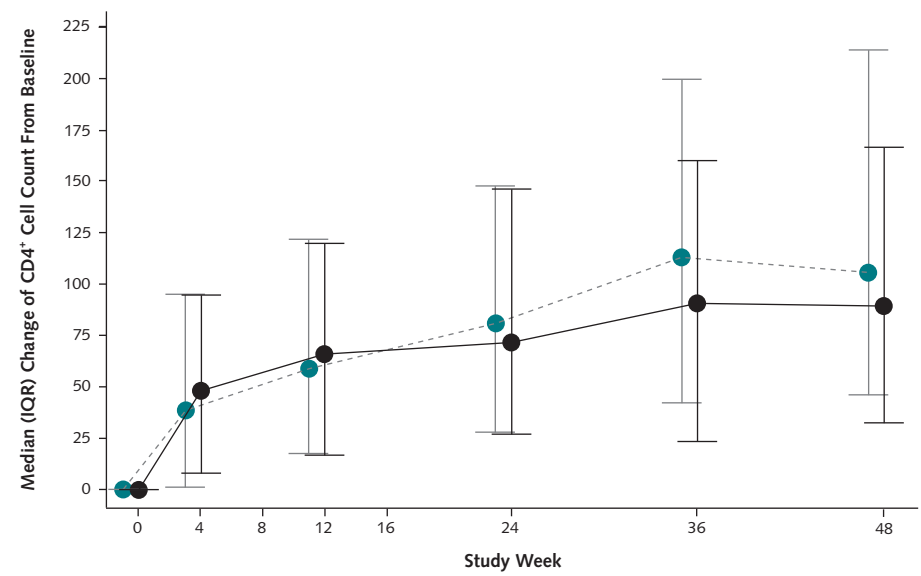
uted to NRTI toxicities. The small number of events limits our ability to conclude that omitting NRTIs leads to reduced mortality.

Our study has limitations. The role of adding NRTIs to a regimen when the cPSS is 2.0 or less was not analyzed. Adding NRTIs may be helpful in persons whose available regimens have with a cPSS less than 2.0. In addition, the minimum number of active antiretroviral drugs required in an optimized regimen without NRTIs is unknown. These results may not apply to resource-poor settings in which genotypic or phenotypic testing and tropism assays are not available. Finally, study treatment was not blinded to participants and investigators.

Figure 4. Observations in each group per study week.



Observations, *n*								
Omit NRTIs	174	172	171	176	171	171	170	165
Add NRTIs	173	178	174	167	173	170	166	169



Observations, *n*						
Omit NRTIs	179	173	175	167	169	163
Add NRTIs	181	178	170	169	165	166

95% CIs are calculated using normal approximation to the binomial. All participants in each randomized group were assessed at baseline (omit-NRTIs group, *n* = 179; add-NRTIs group, *n* = 181). IQR = interquartile range; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor. **Top.** Proportion of participants with HIV-1 RNA level <50 copies/mL. Missing RNA values were excluded. The point estimates (*circles*) and 95% pointwise CIs (*vertical lines*) are shown. **Bottom.** $CD4^+$ cell count changes from baseline for the randomized study groups. The median change (*circles*) and IQR (*vertical lines*) are plotted by scheduled study visit.

Long-term toxicities of NRTIs include decreased bone mineral density, nephrotoxicity, and potential increased risk for myocardial infarction (19–21). Over 48 weeks, however, we did not observe a significant reduction in adverse events in the omit-NRTIs group.

In patients who have previously received antiretroviral drugs, NRTIs can be safely omitted from new active regimens provided that the cumulative activity of the regimen exceeds that of 2 fully active agents as measured by current genotypic and phenotypic testing and tropism assays; prior treatment history must also be accounted for. The potential benefits of omitting NRTIs include reduced pill burden; reduced cost; and, probably, a decrease in NRTI-associated toxicity over the long term. These results have been incorporated in recent antiretroviral guideline recommendations for treatment-experienced patients (2).

From The Miriam Hospital, Alpert Medical School of Brown University, Providence, Rhode Island; Harvard T.H. Chan School of Public Health and Massachusetts General Hospital, Boston, Massachusetts; University of Cincinnati College of Medicine, Cincinnati, Ohio; Johns Hopkins Hospital, Baltimore, Maryland; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Birmingham Veterans Affairs Medical Center, Birmingham, Alabama; National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; West Virginia University School of Medicine, Morgantown, West Virginia; University of Puerto Rico, San Juan, Puerto Rico; Weill Cornell Medical College, New York, New York; and Gilead Sciences, Foster City, California.

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Reproducible Research Statement: *Study protocol*: See the Supplement (available at www.annals.org). *Statistical code and data set*: Available upon request from sdac.data@sdac.harvard.edu with written agreement from the AIDS Clinical Trials Group.

Requests for Single Reprints: Karen T. Tashima, MD, The Miriam Hospital, Alpert Medical School of Brown University, 164 Summit Avenue, Providence, RI 02906; e-mail, ktashima@lifespan.org.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Tashima: The Miriam Hospital, Alpert Medical School of Brown University, 164 Summit Avenue, Providence, RI 02906.
Ms. Smeaton and Mr. Ritz: Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115.
Dr. Fichtenbaum: University of Cincinnati College of Medicine, 231 Albert Sabin Way, PO Box 670560, Cincinnati, OH 45267.
Dr. Andrade: Johns Hopkins Hospital, 600 North Wolfe Street, Sheikh Zayed Tower, Baltimore, MD 21287.
Dr. Eron: Division of Infectious Diseases, University of North Carolina at Chapel Hill, CB 7030, Bioinformatics Building, 130 Mason Farm Road, 2nd Floor, Chapel Hill, NC 27599.
Dr. Gandhi: Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114.
Dr. Johnson: Birmingham Veterans Affairs Medical Center, 700 South 19th Street, Birmingham, AL 35233.
Dr. Klingman: National Institute of Allergy and Infectious Diseases, Therapeutics Research Program, HIV Research Branch, 6700 B Rockledge Drive, Room 9E40A, MSC 7624, Bethesda, MD 20892.
Dr. Hodder: West Virginia University School of Medicine, 1 Medical Center Drive, PO Box 9100, Morgantown, WV 26506.
Dr. Santana: University of Puerto Rico, Medical Sciences Campus, Box 365067, San Juan, Puerto Rico 00936.
Dr. Wilkins: Center for Special Studies (HIV/AIDS), Weill Cornell Medical College, 525 East 68th Street, Floor 24, New York, NY 10065.
Dr. Haubrich: Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404.

Author Contributions: Conception and design: K.T. Tashima, L.M. Smeaton, C.J. Fichtenbaum, A. Andrade, J.J. Eron, R.T. Gandhi, V.A. Johnson, K.L. Klingman, R.H. Haubrich.
Analysis and interpretation of the data: K.T. Tashima, L.M. Smeaton, C.J. Fichtenbaum, A. Andrade, J.J. Eron, R.T. Gandhi, V.A. Johnson, K.L. Klingman, J. Ritz, J.L. Santana, T. Wilkin, R.H. Haubrich.
Drafting of the article: K.T. Tashima, L.M. Smeaton, C.J. Fichtenbaum, R.T. Gandhi, V.A. Johnson, K.L. Klingman, J. Ritz, S. Hodder, R.H. Haubrich.
Critical revision of the article for important intellectual content: L.M. Smeaton, C.J. Fichtenbaum, A. Andrade, J.J. Eron, R.T. Gandhi, V.A. Johnson, S. Hodder, J.L. Santana, R.H. Haubrich.
Final approval of the article: K.T. Tashima, L.M. Smeaton, C.J. Fichtenbaum, A. Andrade, J.J. Eron, R.T. Gandhi, V.A. Johnson, K.L. Klingman, J. Ritz, S. Hodder, J.L. Santana, T. Wilkin, R.H. Haubrich.
Provision of study materials or patients: C.J. Fichtenbaum, J.J. Eron, S. Hodder, J.L. Santana, T. Wilkin, R.H. Haubrich.
Statistical expertise: L.M. Smeaton, J. Ritz.
Obtaining of funding: R.H. Haubrich.
Administrative, technical, or logistic support: V.A. Johnson.
Collection and assembly of data: C.J. Fichtenbaum, J.J. Eron, R.T. Gandhi, V.A. Johnson, J. Ritz, T. Wilkin, R.H. Haubrich.

Appendix: Study Sites and Grant Numbers

New Jersey Medical School Clinical Research Center Clinical Research Site (CRS) (site 31477)

Cornell Chelsea CRS 7804, AIDS Clinical Trial Group (ACTG) Clinical Trials Unit (CTU) grant UM1AI069419; Clinical Trial Center CTC grant UL1TR000457

Cincinnati CRS (site 2401) ACTG CTU grant 2UM1AI069501

Puerto Rico AIDS Clinical Trials Unit CRS (site 5401) ACTG CTU grant 5UM1AI069415-07

University of Southern California CRS (site 1201) ACTG CTU grant AI069432

MetroHealth CRS (site 2503) ACTG grant AI69501

Chapel Hill CRS (site 3201) ACTG CTU grant UM1 AI069423-08; Clinical and Translational Science Award (CTSA) grant 1UL1TR001111; Centers for AIDS Research (CFAR) grant P30 AI50410

Vanderbilt Therapeutics CRS (site 3652) ACTG CTU grant 2UM1AI069439-08; supported in part by the Vanderbilt CTSA grant UL1 TR000445 from National Center for Advancing Translational Sciences/National Institutes of Health

The Miriam Hospital CRS (site 2951) ACTG CTU grant 2UM1A1069412-08

University of California, San Diego Antiviral Research Center CRS (site 701) ACTG CTU grant AI069432

University of Pittsburgh (site 1001) ACTG CTU grant UM1-AI069494

Case Western CRS (site 2501) ACTG CTU grant AI069501

Wayne State University CRS (site 31478) ACTG CTU grant 2UM1AI069503-08

Beth Israel Deaconness Medical Center ACTG CRS (site 103)

Washington University Therapeutics (WT) CRS (site 2101) ACTG CTU grant U01 AI69439-08

Rush University CRS (site 2702) ACTG CTU grant AI-069471

San Juan City Hospital Puerto Rico National Institute of Child Health and Human Development (NICHD) CRS (site 5031) HHSN275201300003C

Duke University Medical Center Adult CRS (site 1601) ACTG CTU grant 5UM1-AI069484-07

Georgetown University CRS (GU CRS) (site 1008)

Ohio State University CRS (site 2301) ACTG CTU grant UM1AI069494

Penn Therapeutics CRS (site 6201) ACTG CTU grant UM1-AI069534-08; CFAR grant 5-P30-AI-045008-15

Northwestern University CRS (site 2701) ACTG CTU grant 5U01 AI069471

Massachusetts General Hospital (MGH) CRS (site 101) ACTG CTU grant 2UM1AI069412-08

HIV/AIDS CRS/Bellevue ACTU site (site 0401) ACTG CTU grant UM1 AI069532

Denver Public Health CRS (site 31470) ACTG CTU grant UM1 AI069503

Henry Ford Hospital CRS (site 31472) ACTG CTU grant 1U01AI069503

Cooper University Hospital CRS (site 31476) ACTG CTU grant UM1 AI069503

University of California, San Francisco HIV/AIDS CRS (site 801) ACTG CTU grant UM1 AI069496

University of Rochester ACTG CRS/AIDS CARE CRS (site 1101/1108) ACTU grant 2UMIAI069511-08; CRC: UL1 RR024160

Howard University Washington DC NICHD CRS (site 5044)

Alabama Therapeutics CRS (site 5801) ACTG CTU grant 2UM1AI069452-08

University of Puerto Rico Pediatric HIV/AIDS Research Program CRS (site 6601)

Bronx-Lebanon Hospital Center CRS (site 31469)

New Jersey Medical School CRS (site 2802) 5UO1AI69537-07

The Ponce de Leon Center CRS (site 5802) ACTG CTU grant 2UM1AI069418; CFAR grant P30A1050409

University of Colorado Hospital CRS (site 6101) ACTG CTU grant 2UM1AI069432; Colorado Clinical Translational Science Institute grant UL1 TR001082

Houston AIDS Research Team CRS (site 31473) ACTG CTU grant UM1 AI068636-08

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UCLA CARE Center CRS (site 601) ACTG CTU grant A1069424

Columbia Physicians and Surgeons CRS (site 30329) ACTG CTU grant 2UM1-AI069470-08; CTSA grant 5UL1 RR024156

Boston Medical Center CRS (site 104) ACTG CTU grant 1U01AI069472-01

UCLA-Los Angeles/Brazil AIDS Consortium (LABAC) CRS (site 3601)

NYU NY NICHD CRS (site 5012)

Miller Children's Hospital Long Beach CA NICHD CRS (site 5093)

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University of Washington AIDS CRS (site 1401) ACTG CTU grant UM1 AI069481

Texas Children's Hospital CRS (site 3801)

Columbia IMPAACT CRS (site 4101)

HIV Baltimore Treatment CRS (site 4651) ACTG CTU grant U01AI069447

Boston Medical Center Pediatric HIV Program NICHD CRS (site 5011)

University of Southern California, Los Angeles (USC LA) NICHD CRS (site 5048)

USC LA NICHD CRS (site 5091)

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Stanford CRS (site 501) ACTG CTU grant AI069556

Pediatric Perinatal HIV CRS (site 4201)

Tulane University New Orleans NICHD CRS (site 5095)

St. Jude Children's Hospital CRS (site 6501)

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Appendix Table 1. PSS Assignment

Drug	PSS = 1	PSS = 0	PSS Calculation
Enfuvirtide	Naive to drug	Ever used enfuvirtide	NA
Maraviroc	Naive to drug class and R5 tropic only	Ever used drug in CCR5 inhibitor class or any evidence of CXCR4 coreceptor use (X4 or dual/mixed tropism) or unable to obtain a result from tropism assay	NA
Raltegravir	Naive to class	Ever used drug in integrase inhibitor class	NA
Darunavir–ritonavir	FC <10	FC ≥90	If FC ≥10 and <90, then PSS = 1 − [(FC − 10)/(90 − 10)]
Tipranavir–ritonavir	FC <2	FC ≥8	If FC ≥2 and <8, then PSS = 1 − [(FC − 2)/(8 − 2)]
Etravirine	FC <2.9	FC ≥10	If FC ≥2.9 and <10, then PSS = 1 − [(FC − 2.9)/(10 − 2.9)]

FC = fold change; NA = not available; PSS = phenotypic susceptibility score.

Appendix Table 2. Inclusion and Exclusion Criteria for OPTIONS Study

4.1 Inclusion Criteria: Step 1

4.1.1 HIV-1 infection documented by a rapid HIV test or any licensed ELISA test kit and confirmed by a repeated ELISA, Western blot, or plasma HIV-1 RNA at any time before study entry.

4.1.2 Antiretroviral experience or resistance at any time in the potential participant's lifetime, including the following:

Prior use of more than 1 NRTI for at least 3 mo and prior use of at least 1 NNRTI for at least 3 mo.

Or

Demonstration of at least 1 mutation from each of the NRTI and NNRTI class lists below on any historical resistance assay.

NRTI-associated mutations: M41L, A62V, K65R, D67N, 69 Insertion Complex, K70R, K70E, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E.

NNRTI-associated mutations: L100I, K103N, V106A/M, V108I, Y181C/I, Y188L/C/H, G190S/A, P225H.

4.1.2 Currently on a failing PI-containing regimen that includes at least 2 other ARVs besides the PI, with no regimen change for the 8 wk before screening.

Note: Within the 8 wk before screening, an alteration in dose, dose frequency, or any within-class substitution(s) for intolerance is permitted, as are drug interruptions for fewer than 7 cumulative days.

4.1.2 Plasma HIV-1 RNA level ≥1000 copies/mL obtained within 30 d before entry on the current regimen using any FDA-approved HIV-1 RNA quantification assay from a laboratory that possesses CLIA certification or its equivalent.

4.1.2 Negative result from a hepatitis B surface antigen test performed within 90 d before study entry.

Note: If a participant was ever hepatitis B surface antigen–or HBV DNA–positive in the past but is currently negative, then he/she must also have positive hepatitis B surface antibody to be eligible.

4.1.2 The following laboratory values obtained within 30 d before Step 1 entry:

ANC ≥750/mm^3

Hemoglobin ≥7.5 g/dL

Platelet count ≥40 000/mm^3

CrCl ≥50 mL/min, as estimated by the Cockcroft–Gault equation*

AST, ALT, and alkaline phosphatase ≤5 × ULN

Total bilirubin ≤2.5 × ULN

Note: If the potential participant is taking an indinavir- or atazanavir-containing regimen at the time of screening, total bilirubin ≤5 × ULN is acceptable.

4.1.2 Women of reproductive potential (women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 mo, or women who have not undergone surgical sterilization, specifically hysterectomy, or bilateral oophorectomy or tubal ligation) will need a negative serum or urine pregnancy test within 30 d before entry.

Note: Acceptable documentation of hysterectomy and bilateral oophorectomy, tubal ligation, tubal microinserts, and menopause is self-reported history.

4.1.2 All potential participants must agree not to participate in the conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, the participant/partner must use at least 2 reliable methods of contraception (condoms, with or without a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormone-based contraceptive) while receiving study treatment and for 6 wk after stopping study treatment.

4.1.2 Men and women aged ≥16 y.

4.1.2 Karnofsky score of ≥70% within 30 d before entry.

4.1.2 Willingness of participant to adhere to protocol requirements, especially with respect to randomized treatment assignment.

4.1.2 Ability to obtain prescription for NRTIs and ritonavir and to have required prescriptions filled at time of entry to Step 2.

4.1.2 Ability and willingness of participant or legal guardian/representative to provide informed consent.

4.1.2 $CD4^+$ cell count result from a specimen drawn within 120 d before study entry; the date of specimen draw and $CD4^+$ cell count must be recorded.

4.1.2 If any previous successful HIV-1 viral coreceptor tropism result is available, then the following information must be recorded:

(a) Most recent specimen date and the tropism result of that specimen (i.e., R5, X4, or D/M)

(b) Specimen date and tropism result of any test with either X4 or D/M result, if different from the specimen in (a).

Note: If multiple previous X4 or D/M results are available, the most recent is recorded.

4.2 Exclusion Criteria: Step 1

4.2.1 Chronic active HBV infection (hepatitis B surface antigen–positive or HBV DNA–positive).

4.2.1 Breastfeeding.

4.2.1 Anticipated requirement on Step 2 for prohibited medications listed in the A5241 MOPS.

Note: Participants who are currently taking any of the prohibited medications but who are able and willing to discontinue them at least 2 wk before entering Step 2 are eligible.

4.2.4 Known allergy/sensitivity or any hypersensitivity to components of 2 or more study-provided drugs or their formulation.

Note: For maraviroc, known hypersensitivity or history of allergy to any component includes hypersensitivity or history of allergy to soy lecithin or peanuts.

4.2.5 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence or participant with study requirements.

4.3 Inclusion Criteria: Step 2

4.3.1 Receipt of successful phenotype/genotype resistance results from a plasma sample obtained at screening (sample obtained no earlier than 105 d before Step 2 entry) and tested at Monogram.

Note: Absence of results from a successful HIV-1 coreceptor tropism assay will not exclude a participant from Step 2 but will make him/her ineligible to receive maraviroc on study. A valid result from a Monogram Trofile tropism assay conducted within 90 d before Step 1 screening, if available, may be used in place of an unsuccessful tropism assay performed after Step 1 entry.

4.3.2 Identification of a study regimen and at least 2 NRTIs for use on study, selected from the options provided by the protocol regimen team.

Note: The selection must be reviewed and approved in writing by the site investigator. The investigator must also provide rationale for the selection.

4.3.2 For the entire duration of Step 1, on the same failing PI-containing regimen that includes at least 2 other ARVs besides the PI.

Note: During Step 1, an alteration in dose, dose frequency, or any within-class substitution(s) for intolerance is permitted, as are drug interruptions for fewer than 7 cumulative days.

Continued on following page

Appendix Table 2–Continued

4.3.2 The following laboratory values obtained within 14 d before Step 2 entry:
ANC ≥750/mm^3
Hemoglobin ≥7.5 g/dL
Platelet count ≥40 000/mm^3
CrCl ≥50 mL/min, as estimated by the Cockcroft-Gault equation*
AST, ALT, and alkaline phosphatase ≤5 × ULN
Total bilirubin ≤2.5 × ULN
Note: If the participant is taking an indinavir- or atazanavir-containing regimen at the time of screening, total bilirubin can be ≤5 × ULN.

4.3.2 Women of reproductive potential (women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 mo, or women who have not undergone surgical sterilization, specifically hysterectomy, or bilateral oophorectomy or tubal ligation) will need a negative serum or urine pregnancy test within 14 d before entering Step 2.

Note: Acceptable documentation of hysterectomy and oophorectomy, tubal ligation, tubal microinserts, and menopause is self-reported history.

4.3.2 All participants must agree not to participate in the conception process (e.g., active attempt to become pregnant, in vitro fertilization), and, if participating in sexual activity that could lead to pregnancy, the participant/partner must use at least 2 reliable methods of contraception (condoms, with or without a spermicidal agent, diaphragm or cervical cap with spermicide, an IUD; or a hormone-based contraceptive) while receiving study treatment and for 6 wk after stopping study treatment.

4.3.2 Karnofsky score of ≥70% within 30 d before entry.

4.4 Exclusion Criteria: Step 2

4.4.1 At or beyond day 76 in Step 1.

4.4.2 Breastfeeding.

4.4.3 Use of any immunomodulator (e.g., interferons, interleukins, systemic corticosteroids, cyclosporine), vaccine, or investigational therapy within 30 d before entering Step 2.

Note A: Use of systemic or inhaled corticosteroids for acute therapy for PCP or asthma exacerbation and prednisone ≤10 mg (or equivalent) is permitted as a stable or tapering dose.

Note B: Administration of vaccinations (e.g., flu vaccine) should also be avoided within 30 d before Step 2 entry but is not exclusionary.

4.4.4 Current use or requirement for any medications prohibited with study treatment. (Lists of prohibited medications are contained in the A5241 MOPS.)

Note: Participants who are currently taking any of the prohibited medications but who are able and willing to discontinue them at least 2 wk before entering Step 2 are eligible.

4.4.4 Serious illness requiring systemic treatment and/or hospitalization until candidate either completes therapy or, in the opinion of the site investigator, is clinically stable on therapy for at least 14 d before entering Step 2.

4.4.4 Inability to qualify for a regimen with a cPSS >2.0 once Group C is closed to enrollment.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARV = antiretroviral; AST = aspartate aminotransferase; CLIA = Clinical Laboratory Improvement Amendments; cPSS = continuous phenotypic susceptibility score; CrCl = creatinine clearance; ELISA = enzyme-linked immunosorbent assay; FDA = U.S. Food and Drug Administration; HBV = hepatitis B virus; IUD = intrauterine device; MOPS = manual of operations; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; OPTIONS = Omitting NRTI from ARV Regimens Is Not Inferior to Adding NRTI in Treatment-Experienced HIV+ Subjects Failing a Protease Inhibitor Regimen; PCP = *Pneumocystis carinii* pneumonia; PI = protease inhibitor; ULN = upper limit of normal.
* Calculation for the Cockcroft-Gault equation is available at www.fstrf.org/common/utilities/calculators/ccc.html.

Appendix Table 3. Study Regimens Dispensed

Regimen	Omit NRTIs (*n* = 179)	Add NRTIs (*n* = 181)	Total (*n* = 360)
Antiretroviral regimens, *n (%)*			
RAL + DRV/R + ETR	99 (55)	102 (56)	201 (56)
RAL + DRV/R + MVC	23 (13)	27 (15)	50 (14)
RAL + DRV/R + ETR + MVC	17 (9)	14 (8)	31 (9)
RAL + ETR + MVC	13 (7)	14 (8)	27 (8)
RAL + DRV/R + ETR + ENF	12 (7)	12 (7)	24 (7)
Other	15 (8)	12 (7)	27 (8)
NRTIs, *n (%)**			
TDF + (3TC or FTC)	143 (80)	149 (82)	292 (81)
TDF + (3TC or FTC) + ZDV	27 (15)	22 (12)	49 (14)
Other	9 (5)	11 (6)	20 (6)

3TC = lamivudine; DRV/R = darunavir plus ritonavir; ENF = enfuvirtide; ETR = etravirine; FTC = emtricitabine; MVC = maraviroc; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; RAL = raltegravir; TDF = tenofovir; ZDV = zidovudine.
* The NRTIs were selected before randomization. For the omit-NRTIs group, participants chose the listed NRTIs but did not initiate NRTIs at baseline.

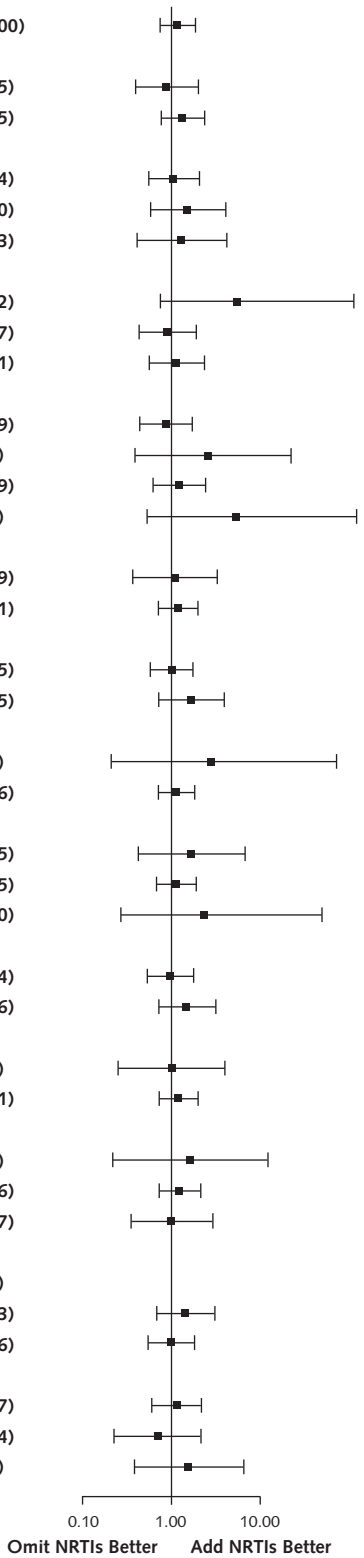
Appendix Table 4. Reasons for NRTI Strategy Discontinuation, by Randomized Group*

Reason for Strategy Discontinuation†	Omit NRTIs (*n* = 19)	Add NRTIs (*n* = 10)	Total (*n* = 29)
Withdrew consent/participant decision	2 (11)	2 (20)	4 (14)
Loss to follow-up	3 (16)	1 (10)	4 (14)
Desire to change regimen	4 (21)	0 (0)	4 (14)
Toxicity/intolerance	0 (0)	2 (20)	2 (7)
Not adherent to study regimen or visits	4 (21)	1 (10)	5 (17)
Reduce number of pills taken	0 (0)	2 (20)	2 (7)
Hepatitis B	2 (11)	0 (0)	2 (7)
Nonadherent to NRTI strategy	1 (5)	2 (20)	3 (10)
Inadequate virologic or immune response	2 (11)	0 (0)	2 (7)
Clinical progression	1 (5)	0 (0)	1 (3)

NRTI = nucleoside or nucleotide reverse transcriptase inhibitor.
* Values are numbers (percentages).
† Of these, 16 triggered the primary efficacy outcome of regimen failure (10 in the omit-NRTIs group and 6 in the add-NRTIs group).

Appendix Figure. Composite primary outcome of regimen failure, by subgroup.

Variable	Patients, *n* (%)		Odds Ratio (95% CI)	Interaction *P* Value
	Omit NRTIs (*n* = 179)	Add NRTIs (*n* = 181)		
Overall	179 (100)	181 (100)	1.17 (0.74–1.85)	0.51
Sex				0.43
Women	47 (26)	46 (25)	0.88 (0.39–2.01)	
Men	132 (74)	135 (75)	1.33 (0.75–2.36)	
Race/ethnicity				0.83
Non-Hispanic black	69 (39)	79 (44)	1.06 (0.55–2.05)	
Hispanic (regardless of race)	46 (26)	37 (20)	1.51 (0.58–4.09)	
Non-Hispanic white	55 (31)	59 (33)	1.29 (0.40–4.26)	
NRTI susceptibility among chosen NRTI				0.32
0	18 (10)	21 (12)	5.71 (0.75–118.3)	
1	100 (56)	103 (57)	0.90 (0.43–1.88)	
2	61 (34)	57 (31)	1.14 (0.55–2.35)	
Baseline viral tropism				0.43
Dual-mixed	72 (40)	71 (39)	0.86 (0.43–1.73)	
Not reported	11 (6)	11 (6)	2.57 (0.38–22.75)	
CCR5	88 (49)	89 (49)	1.22 (0.61–2.45)	
CXCR4	8 (4)	10 (6)	5.40 (0.53–126.7)	
ENF- or INSTI-experience stratification factor				0.89
Most difficult (ENF- or INSTI-experienced)	32 (18)	34 (19)	1.09 (0.36–3.25)	
Not most difficult (ENF- and INSTI-naive)	147 (82)	147 (81)	1.18 (0.71–1.97)	
MVC use stratification factor				0.33
Regimen excludes MVC	118 (66)	118 (65)	1.00 (0.57–1.74)	
Regimen includes MVC	61 (34)	63 (35)	1.64 (0.71–3.88)	
NRTI susceptibility stratification factor				0.51
0 NRTIs susceptible	7 (4)	8 (4)	2.80 (0.21–70.82)	
≥1 NRTIs susceptible	172 (96)	173 (96)	1.13 (0.71–1.81)	
Study antiretroviral cPSS score				0.75
<3	22 (12)	27 (15)	1.65 (0.43–6.66)	
3	132 (74)	136 (75)	1.12 (0.67–1.87)	
>3	25 (14)	18 (10)	2.32 (0.27–49.17)	
Number of new drug classes				0.39
1	102 (57)	97 (54)	0.97 (0.53–1.77)	
>1	77 (43)	84 (46)	1.48 (0.71–3.10)	
Number of new study antiretroviral drugs				0.81
1, 2	17 (9)	17 (9)	1.00 (0.25–3.98)	
3, 4	162 (91)	164 (91)	1.20 (0.72–1.99)	
Number of classes of antiretroviral drugs used previously				0.90
2	6 (3)	13 (7)	1.60 (0.22–12.07)	
3	135 (75)	137 (76)	1.23 (0.72–2.11)	
4	38 (21)	31 (17)	1.00 (0.35–2.88)	
Entry inhibitors among chosen study regimen				0.76
Both ENF and MVC	3 (2)	2 (1)		
Either ENF or MVC	77 (43)	77 (43)	1.43 (0.68–3.05)	
Neither ENF or MVC	99 (55)	102 (56)	1.00 (0.55–1.81)	
Pansensitivity				0.65
Sensitive to 1 or 0 drug classes	131 (73)	140 (77)	1.14 (0.60–2.18)	
Sensitive to 2 drug classes	30 (17)	25 (14)	0.71 (0.23–2.13)	
Sensitive to 3 drug classes	18 (10)	16 (9)	1.56 (0.39–6.46)	



Point estimates (*squares*) and 95% CIs (*horizontal lines*) of the odds ratios of regimen failure for the omit- versus add-NRTIs groups are displayed. Numbers in the right column are the overall treatment and subgroup interaction *P* values. cPSS = continuous phenotypic susceptibility score; ENF = enfuvirtide; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor.

Appendix Table 5. Grade 3 or 4 Signs or Symptoms Occurring in at Least 5% of Participants*

Grade 3 or 4 Sign/Symptom for Categories Occurring in at Least More than 5% of Participants or Events of Interest	Omit NRTIs (*n* = 177)	Add NRTIs (*n* = 180)	Total (*n* = 357)
Any sign or symptom	35 (20)	48 (27)	83 (23)
Any general body	21 (12)	31 (17)	52 (15)
Pain	16 (9)	24 (13)	40 (11)
Any respiratory	4 (2)	13 (7)	17 (5)
Any gastrointestinal	6 (3)	7 (4)	13 (4)
Diarrhea/loose	1 (1)	4 (2)	5 (1)
Vomiting	4 (2)	2 (1)	6 (2)
Any renal	1 (1)	2 (1)	3 (1)
Renal or urinary system dysfunction	0 (0)	2 (1)	2 (1)
Any skin	6 (3)	6 (3)	12 (3)
Any neurologic	10 (6)	11 (6)	21 (6)
Depression	4 (2)	2 (1)	6 (2)
Headache	2 (1)	3 (2)	5 (1)
Mental status changes, psychiatric, specify	3 (2)	2 (1)	5 (1)

NRTI = nucleoside or nucleotide reverse transcriptase inhibitor.
* Values are numbers (percentages). Events of interest (determined post hoc) are also displayed even when less than 5%.

Appendix Table 6. Baseline and Change From Baseline to 48 Weeks in Calculated Creatinine Clearance and Lipid Values, by Study Group

Value	Omit NRTIs		Add NRTIs		*P* Value
	Participants, *n*	Median (IQR)	Participants, *n*	Median (IQR)	
Creatinine clearance (mL/s)					0.23
Baseline	178	1.80 (1.44 to 2.24)	181	1.79 (1.47 to 2.12)	
Change at week 48	163	−0.02 (−0.18 to 0.13)	170	−0.07 (−0.18 to 0.07)	
Total cholesterol (all samples, mmol/L)					
Baseline	161	4.25 (3.63 to 4.84)	161	4.25 (3.55 to 4.97)	
Change at week 48	144	0.57 (0.10 to 1.14)	146	0.26 (−0.36 to 0.85)	
HDL cholesterol (fasting only, mmol/L)					
Baseline	152	0.98 (0.78 to 1.27)	152	37 (0.78 to 1.19)	
Change at week 48	119	0.10 (0.03 to 0.23)	126	0.05 (−0.08 to 0.21)	
Non-HDL cholesterol (fasting only, mmol/L)					0.003
Baseline	149	3.21 (2.62 to 3.86)	153	3.39 (2.64 to 4.04)	
Change at week 48	117	0.39 (0 to 1.01)	125	0.18 (−0.47 to 0.75)	
Triglycerides (fasting only, mmol/L)					
Baseline	153	1.59 (0.99 to 2.45)	154	1.50 (1.08 to 2.70)	
Change at week 48	129	0.01 (−0.33 to 0.55)	134	0.05 (−0.40 to 0.49)	

HDL = high-density lipoprotein; IQR = interquartile range; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor.