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## Class-Sparing Regimens for Initial Treatment of HIV-1 Infection

Sharon A. Riddler, M.D., M.P.H., Richard Haubrich, M.D., A. Gregory DiRienzo, Ph.D., Lynne Peeples, M.S., William G. Powderly, M.D., Karin L. Klingman, M.D., Kevin W. Garren, Ph.D., Tania George, Pharm.D., James F. Rooney, M.D., Barbara Brizz, M.H.S.Ed., B.S.N.,\* Umesh G. Laloo, M.D., Robert L. Murphy, M.D., Susan Swindells, M.B., B.S., Diane Havlir, M.D., and John W. Mellors, M.D.,  
for the AIDS Clinical Trials Group Study A5142 Team†

### ABSTRACT

#### BACKGROUND

The use of either efavirenz or lopinavir–ritonavir plus two nucleoside reverse-transcriptase inhibitors (NRTIs) is recommended for initial therapy for patients with human immunodeficiency virus type 1 (HIV-1) infection, but which of the two regimens has greater efficacy is not known. The alternative regimen of lopinavir–ritonavir plus efavirenz may prevent toxic effects associated with NRTIs.

#### METHODS

In an open-label study, we compared three regimens for initial therapy: efavirenz plus two NRTIs (efavirenz group), lopinavir–ritonavir plus two NRTIs (lopinavir–ritonavir group), and lopinavir–ritonavir plus efavirenz (NRTI-sparing group). We randomly assigned 757 patients with a median CD4 count of 191 cells per cubic millimeter and a median HIV-1 RNA level of 4.8 log<sub>10</sub> copies per milliliter to the three groups.

#### RESULTS

At a median follow-up of 112 weeks, the time to virologic failure was longer in the efavirenz group than in the lopinavir–ritonavir group ( $P=0.006$ ) but was not significantly different in the NRTI-sparing group from the time in either of the other two groups. At week 96, the proportion of patients with fewer than 50 copies of plasma HIV-1 RNA per milliliter was 89% in the efavirenz group, 77% in the lopinavir–ritonavir group, and 83% in the NRTI-sparing group ( $P=0.003$  for the comparison between the efavirenz group and the lopinavir–ritonavir group). The groups did not differ significantly in the time to discontinuation because of toxic effects. At virologic failure, antiretroviral resistance mutations were more frequent in the NRTI-sparing group than in the other two groups.

#### CONCLUSIONS

Virologic failure was less likely in the efavirenz group than in the lopinavir–ritonavir group. The virologic efficacy of the NRTI-sparing regimen was similar to that of the efavirenz regimen but was more likely to be associated with drug resistance. (ClinicalTrials.gov number, NCT00050895.)

From the University of Pittsburgh, Pittsburgh (S.A.R., J.W.M.); the University of California, San Diego, San Diego (R.H.); the Harvard School of Public Health, Boston (A.G.D., L.P.); University College Dublin, Dublin (W.G.P.); the Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD (K.L.K.); Abbott Laboratories, Abbott Park, IL (K.W.G.); Bristol-Myers Squibb, Plainsboro, NJ (T.G.); Gilead Sciences, Foster City, CA (J.F.R.); Social and Scientific Systems, Silver Spring, MD (B.B.); the University of KwaZulu Natal, Durban, South Africa (U.G.L.); Northwestern University, Chicago (R.L.M.); the University of Nebraska Medical Center, Omaha (S.S.); and the University of California, San Francisco, San Francisco (D.H.). Address reprint requests to Dr. Riddler at 613 Falk Bldg., 3601 Fifth Ave., Pittsburgh, PA 15213, or at riddler@dom.pitt.edu.

Drs. Riddler and Haubrich contributed equally to this article.

\*Deceased.

†Investigators in the AIDS Clinical Trials Group Study A5142 Team are listed in the Appendix.

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CURRENT PRACTICE GUIDELINES RECOMMEND the use of efavirenz or ritonavir-boosted protease inhibitor regimens containing two nucleoside reverse-transcriptase inhibitors (NRTIs) for initial therapy of human immunodeficiency virus type 1 (HIV-1) infection.<sup>1,2</sup> These recommendations are derived from expert opinion and the results of clinical trials, but to our knowledge well-powered, head-to-head comparisons of these regimens have not been performed.<sup>3-5</sup>

Although NRTIs are included in all recommended antiretroviral regimens, toxic effects, especially lipoatrophy associated with the thymidine analogues,<sup>6,7</sup> has raised interest in regimens that do not contain NRTIs. Pilot studies of NRTI-sparing regimens have shown good virologic efficacy, but adequately powered studies comparing these regimens for initial therapy are lacking.<sup>3,8</sup> Therefore, we conducted a multicenter, randomized trial to compare the virologic efficacy, immunologic response, side-effect profile, and metabolic complications of efavirenz plus two NRTIs, of lopinavir-ritonavir plus two NRTIs, and of lopinavir-ritonavir plus efavirenz.

## METHODS

### STUDY POPULATION

The study population consisted of HIV-1-infected male and female patients at least 13 years of age who had not received previous antiretroviral therapy. All patients had a plasma HIV-1 RNA level of at least 2000 copies per milliliter with any CD4 cell count, and acceptable laboratory results. An institutional review board or ethics committee at each site approved the study, and all patients provided written informed consent. The study was monitored by the data and safety monitoring board of the National Institute of Allergy and Infectious Diseases. The authors who were employed by companies that supplied study drugs participated in the trial design, data accrual, data analysis, and manuscript preparation. All authors vouch for the completeness and accuracy of the data.

### STUDY DESIGN

In this phase 3, randomized, multicenter, open-label trial, eligible patients were randomly assigned with equal probability to receive one of

three regimens: 600 mg of efavirenz (Sustiva tablets, Bristol-Myers Squibb) once daily plus two NRTIs (efavirenz group), a combination of 400 mg of lopinavir and 100 mg of ritonavir (Kaletra capsules, Abbott Laboratories) twice daily plus two NRTIs (lopinavir-ritonavir group), or 533 mg of lopinavir and 133 mg of ritonavir twice daily plus 600 mg of efavirenz once daily (NRTI-sparing group).

The NRTIs used in the efavirenz group and the lopinavir-ritonavir group were lamivudine (Epivir, GlaxoSmithKline) for all patients at a dose of 150 mg twice daily or 300 mg once daily plus the choice of one of three other agents: zidovudine (Retrovir, GlaxoSmithKline) at a dose of 300 mg twice daily, stavudine extended release (XR) (Zerit XR, investigational agent, Bristol-Myers Squibb) at a dose of 100 mg once daily (with participants weighing less than 60 kg receiving 75 mg), or tenofovir disoproxil fumarate (DF) (Viread, Gilead Sciences) at a dose of 300 mg once daily. The choice of the second NRTI was made by the site investigator before randomization. Changes in NRTI were not allowed during the study. Lopinavir-ritonavir, efavirenz, stavudine XR, and tenofovir DF were provided by the manufacturer, and other medications were obtained through prescriptions.

Randomization was stratified according to a permuted-block design on the basis of three factors: the screening level of plasma HIV-1 RNA (<100,000 vs. ≥100,000 copies per milliliter), the presence or absence of chronic hepatitis infection (B, C, or both), and the choice of NRTI. After screening, study evaluations were completed before study entry, at entry, and at weeks 1, 4, 8, 12, 16, 20, and 24 and every 8 weeks thereafter for the duration of the study. Plasma HIV-1 RNA was measured at each visit at a central laboratory (Roche Amplicor HIV-1 Monitor assay, ultrasensitive version 1.5). The CD4 cell count was measured before study entry, at entry, and every 8 weeks thereafter.

Patients' adherence to a study-drug regimen was assessed by standardized self-report.<sup>9</sup> The adherence questionnaire included a 4-day recall and several questions that included data on doses that were missed during the past week and those that were missed during the past weekend. At week 12, an adherence rate of 100% was defined as all doses taken during the previous 4 days plus

no other missed doses, as identified by the additional questions. Body composition was measured by whole-body dual-energy x-ray absorptiometry (DEXA) at study entry and at weeks 48 and 96.<sup>10,11</sup> Adverse clinical and laboratory events were assessed by the site investigators and were scored with the use of the adverse-event grading scale of the National Institutes of Health's Division of AIDS (1992 version). The occurrence of clinical lipoatrophy and treatment-limiting toxic effects were determined by the site investigator. Each patient was scheduled for 96 weeks of follow-up after the last enrollment.

Genotyping for resistance to HIV-1 drugs was performed during screening if the site investigator suspected that the patient had been infected with HIV-1 for 1 year or less. Genotyping data were reviewed by the protocol chairs and virologist, and the patient was deemed to be ineligible for the study if any evidence of resistance to a study drug was present.<sup>12</sup> At the time of virologic failure, drug-resistance genotyping was performed in a central laboratory (Quest Diagnostics). The genotype was used by the site investigator to choose a new regimen. Patients were allowed to continue the same regimen if it was deemed to be clinically appropriate.

#### STATISTICAL ANALYSIS

The two primary objectives of the study were to perform pairwise comparisons of the time to virologic failure and the time to regimen failure among the three study groups. Virologic failure was defined as a lack of suppression of plasma HIV-1 RNA by 1 log<sub>10</sub> or rebound before week 32 or a lack of suppression to less than 200 copies per milliliter or rebound after week 32. Confirmation of suspected virologic failure was required within 4 weeks. Data from patients whose confirmation sample was missing were included among failure end points. Regimen failure was defined as the first of either virologic failure or toxicity-related discontinuation of any component of the initial randomized treatment regimen.

All patients who underwent randomization and received at least one dose of a study drug were included in the analysis. All analyses were performed on an intention-to-treat basis and were stratified according to the three randomization factors. Patients who discontinued any therapy because of a toxic effect were followed for

the occurrence of virologic failure. Data from patients who did not have virologic failure or regimen failure while they were taking a study drug were censored at the time of the last study visit. Missing data due to missed evaluations, loss to follow-up, or censoring were ignored. Prespecified subgroup analyses that were based on the randomization strata were conducted after the completion of the two primary analyses.

Distributions of the time from randomization to virologic failure and to regimen failure were estimated with the use of the Kaplan–Meier method and tested for equality with the use of the stratified log-rank test on the basis of the randomization factors. Cox proportional-hazards models were used to estimate hazard ratios and corresponding confidence intervals. The overall type I error rate was 0.05, with 0.017 (0.05 ÷ 3) allocated to each pairwise comparison between study groups; after adjustment for interim analyses, the final type I error rate was 0.014. Thus, only P values of less than 0.014 were considered to have statistical significance in the analyses of primary objectives. The approach outlined by DiRienzo and DeGruttola<sup>13</sup> was used to calculate adjusted P values for simultaneous consideration of both primary outcomes. Three interim analyses were conducted by the data and safety monitoring board. At each interim analysis, 0.003 of the total type I error was spent (0.001 for each of the three pairwise comparisons, on the basis of a Peto stopping rule). All reported P values are two-sided.

As originally designed with a total number of 660 patients, the study had a power of approximately 85% to detect a 56% reduction in the risk of virologic failure and a power of 90% to detect a 52% reduction in the risk of regimen failure. The study remained open to enrollment after reaching the initial target of 660 patients to complete enrollment at the South African site and enrollment in a prespecified substudy of endothelial function.<sup>14</sup>

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## RESULTS

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#### PATIENTS

A total of 757 patients were enrolled from January 2003 to May 2004. The baseline characteristics of the 753 patients who received study drugs are provided in Table 1; 80% of the patients were

**Table 1. Baseline Characteristics of the Patients.\***

Variable	All Patients (N=753)	Efavirenz Group (N=250)	Lopinavir–Ritonavir Group (N=253)	NRTI-Sparing Group (N=250)
Sex — no. (%)				
Male	602 (80)	203 (81)	194 (77)	205 (82)
Female	151 (20)	47 (19)	59 (23)	45 (18)
Race or ethnic group — no. (%)†				
White	274 (36)	99 (40)	88 (35)	87 (35)
Black	314 (42)	96 (38)	116 (46)	102 (41)
Hispanic	146 (19)	46 (18)	44 (17)	56 (22)
Asian	15 (2)	7 (3)	4 (2)	4 (2)
Other or unknown	4 (1)	2 (1)	1 (<1)	1 (<1)
Median age — yr	38	39	37	38
Age group — no. (%)				
13–29 yr	135 (18)	41 (16)	42 (17)	52 (21)
30–39 yr	288 (38)	90 (36)	107 (42)	91 (36)
40–49 yr	241 (32)	90 (36)	81 (32)	70 (28)
50–59 yr	75 (10)	25 (10)	21 (8)	29 (12)
≥60 yr	14 (2)	4 (2)	2 (1)	8 (3)
Median CD4 count — cells/mm <sup>3</sup> ‡	191	195	190	189
CD4 count — no. (%)				
<100 cells/mm <sup>3</sup>	260 (35)	86 (34)	83 (33)	91 (36)
100–199 cells/mm <sup>3</sup>	129 (17)	41 (16)	52 (21)	36 (14)
200–299 cells/mm <sup>3</sup>	151 (20)	51 (20)	53 (21)	47 (19)
300–500 cells/mm <sup>3</sup>	169 (22)	55 (22)	57 (23)	57 (23)
>500 cells/mm <sup>3</sup>	38 (5)	16 (6)	7 (3)	15 (6)
Median baseline HIV-1 RNA — log <sub>10</sub> copies/ml	4.8	4.8	4.8	4.9
HIV-1 RNA level — no. (%)§				
<50,000 copies/ml	311 (41)	114 (46)	107 (42)	90 (36)
50,000–99,999 copies/ml	155 (21)	47 (19)	52 (21)	56 (22)
100,000–299,999 copies/ml	129 (17)	42 (17)	39 (15)	48 (19)
300,000–499,999 copies/ml	53 (7)	15 (6)	22 (9)	16 (6)
≥500,000 copies/ml	105 (14)	32 (13)	33 (13)	40 (16)
Hepatitis B or C — no. (%)¶	102 (14)	35 (14)	33 (13)	34 (14)
NRTI selected — no. (%)				
Zidovudine	317 (42)	105 (42)	106 (42)	106 (42)
Stavudine XR	181 (24)	59 (24)	62 (25)	60 (24)
Tenofovir DF	255 (34)	86 (34)	85 (34)	84 (34)

\* There were no significant differences among the study groups with respect to any baseline characteristic. Percentages may not total 100 because of rounding. DF denotes disoproxil fumarate, NRTI nucleoside reverse-transcriptase inhibitor, and XR extended release.

† Race or ethnic group was self-reported.

‡ The baseline CD4 cell count was calculated as the mean of two measurements obtained at visits before study entry and at entry.

§ HIV-1 RNA was calculated as the mean of two measurements obtained at visits before study entry and at entry.

¶ The presence of hepatitis B or C was determined by the identification of hepatitis B surface antigen or hepatitis C antibody.

men, and 64% were nonwhite. At baseline, the median plasma HIV-1 RNA level was 64,203 (4.8 log<sub>10</sub>) copies per milliliter, and the median CD4 cell count was 191 cells per cubic millimeter. Baseline characteristics of patients were well balanced among the three study groups. Only 5 of 153 participants with available screening data were excluded from enrollment because of HIV-1 drug resistance.

The median follow-up was 112 weeks, with no differences among the study groups. A total of 589 of 753 patients (78%) completed the protocol. Of the remaining 164 patients, 19 died, 56 were unable to attend clinic visits, 26 were unwilling to adhere to the protocol, 46 could not be contacted, and 17 had other reasons. There were no significant differences among the three study groups in the reasons for loss to follow-up or the time until patients were lost to follow-up (P=0.66).

#### PRIMARY OUTCOMES

##### *Virologic Failure*

As defined in the protocol, virologic failure occurred in 60 of 250 patients (24%) in the efavirenz group, 94 of 253 patients (37%) in the lopinavir–ritonavir group, and 73 of 250 patients (29%) in the NRTI-sparing group. The efavirenz group had a significantly longer time to virologic failure than did the lopinavir–ritonavir group (P=0.006) (Fig. 1A and Table 2); the differences between the NRTI-sparing group and the efavirenz group (P=0.49) or the lopinavir–ritonavir group (P=0.13) were not significant.

Among patients with HIV-1 RNA levels of 100,000 copies per milliliter or more at screening, the efavirenz group had a longer time to virologic failure than either the lopinavir–ritonavir group (P=0.01) or the NRTI-sparing group (P=0.02) (Fig. 1B). For patients with HIV-1 RNA levels of less than 100,000 copies per milliliter at screening, the NRTI-sparing group had a longer time to virologic failure than the lopinavir–ritonavir group (P=0.02), but there was no significant difference between the efavirenz group and the lopinavir–ritonavir group (P=0.13) or the NRTI-sparing group (P=0.26) (Fig. 1C). In a multivariable Cox proportional-hazards model stratified according to the three baseline factors, a greater risk of virologic failure was associated with female sex (hazard ratio, 1.38; 95% confi-

dence interval [CI], 1.01 to 1.89), black race as compared with all others (hazard ratio, 1.57; 95% CI, 1.18 to 2.08), a younger age group at baseline, as compared with the next incremental age group (hazard ratio, 1.23; 95% CI, 1.06 to 1.45), and a group with a lower CD4 cell count, as compared with the next incremental cell-count group (hazard ratio, 1.14; 95% CI, 1.01 to 1.27) (Table 1). No other variables were considered in this model.

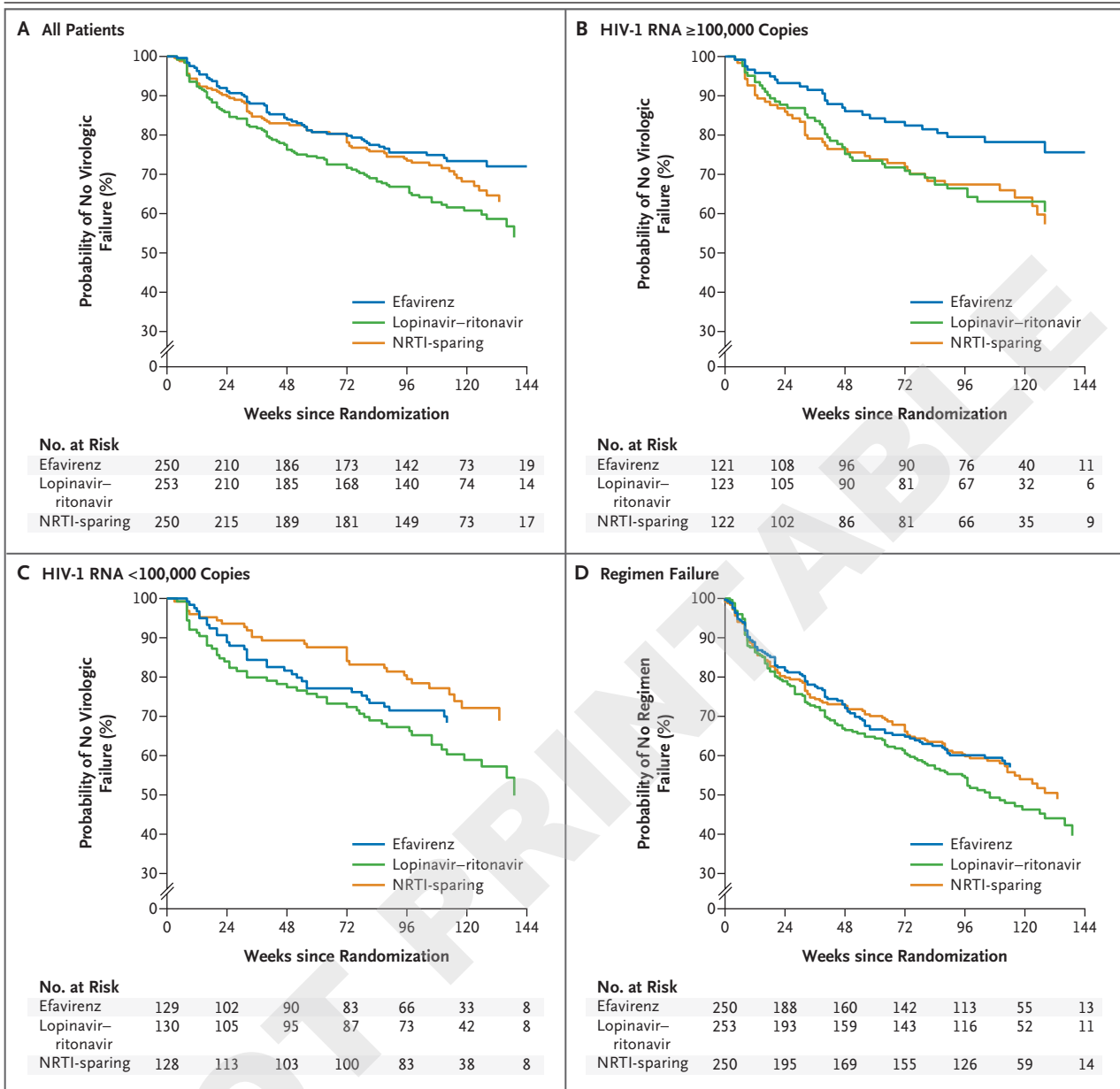
##### *Regimen Failure*

The regimen-failure outcome occurred in 95 of 250 patients (38%) in the efavirenz group, 127 of 253 patients (50%) in the lopinavir–ritonavir group, and 108 of 250 patients (43%) in the NRTI-sparing group. There was a trend toward a longer time to regimen failure in the efavirenz group than in the lopinavir–ritonavir group (P=0.03), but the P value did not reach the significance level of 0.014 with adjustment for multiple comparisons (Fig. 1D and Table 2).

#### RESPONSE TO TREATMENT

At week 96, the proportions of patients with fewer than 200 copies per milliliter of plasma HIV-1 RNA were 93% (95% CI, 88 to 96) in the efavirenz group, 86% (95% CI, 80 to 91) in the lopinavir–ritonavir group, and 92% (95% CI, 87 to 96) in the NRTI-sparing group (Fig. 2A). At the same time, the proportions of patients with fewer than 50 copies per milliliter of plasma HIV-1 RNA were 89% (95% CI, 84 to 93) in the efavirenz group, 77% (95% CI, 71 to 83) in the lopinavir–ritonavir group, and 83% (95% CI, 76 to 88) in the NRTI-sparing group (Fig. 2B). (For the comparison between the efavirenz group and the lopinavir–ritonavir group, P=0.04 for fewer than 200 copies per milliliter and P=0.003 for fewer than 50 copies per milliliter; P>0.05 for each of the other pairwise comparisons.)

A sustained increase in the CD4 cell count after study entry was observed in all three study groups. At week 96, the median increase from baseline was 230 cells per cubic millimeter (interquartile range, 142 to 353) in the efavirenz group, 287 cells per cubic millimeter (interquartile range, 155 to 422) in the lopinavir–ritonavir group, and 273 cells per cubic millimeter (interquartile range, 176 to 419) in the NRTI-sparing group. At week 96, the change from baseline in the CD4 cell count was greater in the lopinavir–ritonavir group



**Figure 1. Time to Virologic Failure and Time to Regimen Failure.**

Shown are the times to virologic failure for the entire study population (Panel A), for patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more (Panel B), and for patients with a screening HIV-1 RNA level of fewer than 100,000 copies per milliliter (Panel C). Panel D shows the time to regimen failure for the entire study population.

and the NRTI-sparing group than in the efavirenz group ( $P=0.01$  for the both comparisons by the Wilcoxon rank-sum test). At week 48, there were no significant differences among the three groups in the change from baseline in the CD4 cell count.

**ADHERENCE TO TREATMENT**

Among patients who were receiving their assigned study drugs at week 12, 405 of 657 (62%) reported having missed no doses since study entry; there were no significant differences among the study groups. Patients in the subgroup with 100% ad-

**Table 2. Hazard Ratios, with 95% Confidence Intervals, for Time to Virologic Failure and Time to Regimen Failure.**

Regimen	Time to Virologic Failure	Time to Regimen Failure
Efavirenz vs. lopinavir–ritonavir	0.63 (0.45–0.87)	0.75 (0.57–0.98)
Efavirenz vs. NRTI-sparing therapy	0.86 (0.61–1.21)	0.93 (0.70–1.23)
Lopinavir–ritonavir vs. NRTI-sparing therapy	1.30 (0.95–1.77)	1.21 (0.93–1.56)

herence had a longer time to virologic failure than did patients whose rate of adherence was lower, regardless of study-group assignment ( $P < 0.001$ ).

**ADVERSE EVENTS**

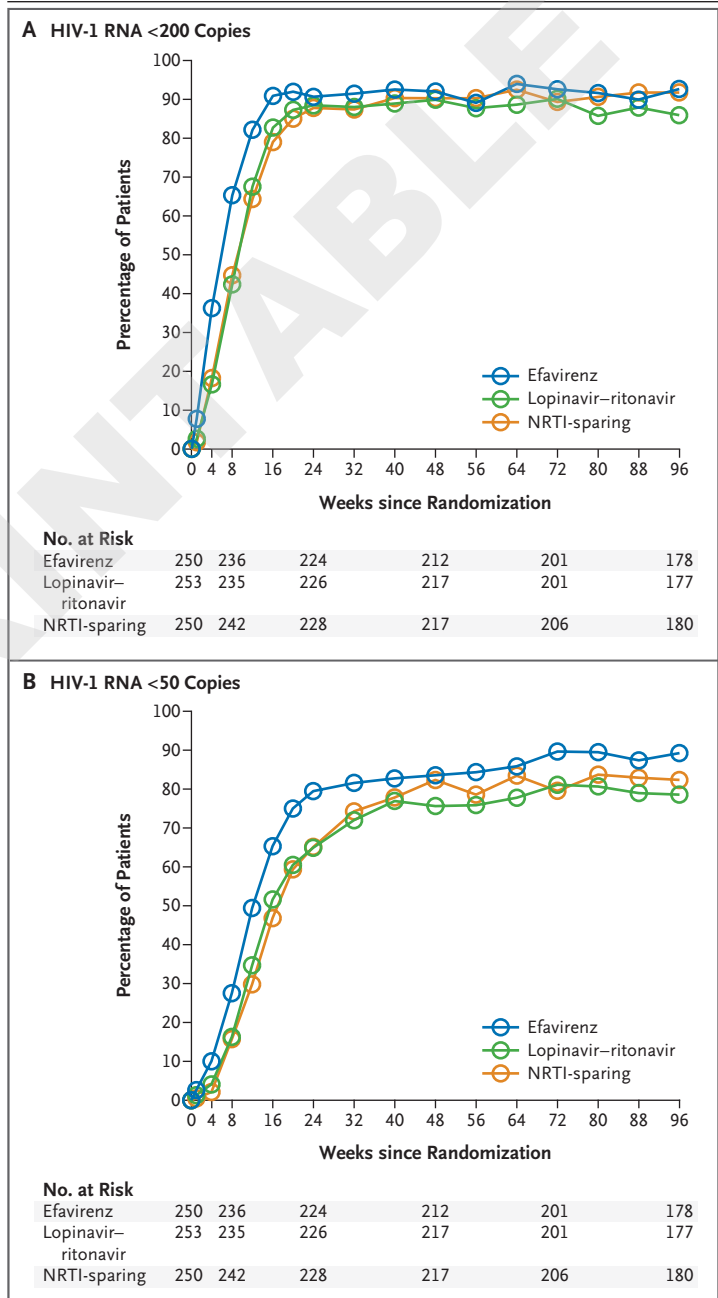
Toxicity leading to discontinuation of one or more drugs in the initial regimen occurred in 134 of 753 patients (18%). There were no significant differences in the time to the first treatment-limiting adverse event among the three study groups. The most frequent treatment-limiting adverse events are summarized in Table 3. There were 19 deaths, one of which was determined to have a probable association with a study drug. This patient was assigned to the NRTI-sparing group and died of hepatotoxicity at week 14 of the study.

From baseline to week 96, the median increase in limb fat as seen on DEXA was 0.05 kg in the the efavirenz group, 0.7 kg in the lopinavir–ritonavir group, and 1.15 kg in the NRTI-sparing group ( $P \leq 0.01$  for each of the three pairwise comparisons). One or more new or recurrent conditions that define the presence of the acquired immunodeficiency syndrome (AIDS) occurred in 9 of 250 patients (4%) in the efavirenz group, 16 of 253 patients (6%) in the lopinavir–ritonavir group, and 15 of 250 patients (6%) in the NRTI-sparing group, but the differences were not significant.

A total of 131 of 753 patients (17%) had a new grade 3 or 4 sign or symptom, and 259 of 753 patients (34%) had a new grade 3 or 4 laboratory abnormality while receiving their assigned regimen (Table 3). The proportion of patients with at least one new grade 3 or 4 laboratory event was higher in the NRTI-sparing group than

**Figure 2. Virologic Response, According to Study Group.**

Shown are the percentage of patients in each study group with an HIV-1 RNA level of fewer than 200 copies per milliliter (Panel A) and the percentage with an HIV-1 RNA level of fewer than 50 copies per milliliter (Panel B).



**Table 3. Treatment-Limiting Adverse Events and New Grade 3 or 4 Clinical Events or Laboratory Abnormalities.\***

Event	Efavirenz Group (N=250)	Lopinavir–Ritonavir Group (N=253)	NRTI-Sparing Group (N=250)
Treatment-limiting event			
Pain or discomfort	10 (4)	5 (2)	3 (1)
Fasting triglycerides†	0	4 (2)	11 (4)
Macules, papules, or rash‡	6 (2)	0	3 (1)
Nausea	3 (1)	7 (3)	3 (1)
Grade 3 or 4 clinical event			
Any new sign or symptom	42 (17)	46 (18)	43 (17)
Pain or discomfort	14 (6)	14 (6)	19 (8)
Diarrhea or loose stool‡	1 (<1)	8 (3)	7 (3)
Nausea	7 (3)	4 (2)	8 (3)
Macules, papules, or rash	6 (2)	2 (1)	7 (3)
Headache	6 (2)	9 (4)	2 (1)
Grade 3 or 4 laboratory abnormality			
Any abnormality†§	72 (29)	80 (32)	107 (43)
Creatine kinase >5 times ULN	8 (3)	8 (3)	14 (6)
Absolute neutrophil count <750/mm <sup>3</sup>	11 (4)	18 (7)	12 (5)
Fasting LDL cholesterol >190 mg/dl§	7 (3)	2 (1)	14 (6)
Fasting triglycerides >750 mg/dl†‡§	6 (2)	16 (6)	34 (14)
Hepatic aminotransferase >5 times ULN†¶	10 (4)	16 (6)	21 (8)
Lipase >2 times ULN‡	22 (9)	11 (4)	12 (5)
Clinical lipatrophy†	8 (3)	3 (1)	0

\* Treatment-limiting events, as determined by the site investigator, were defined as those occurring in 2% or more of patients in any study group. Adverse events are those that occurred in 3% or more of patients in any study group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. LDL denotes low-density lipoprotein, and ULN upper limit of the normal range.

† P<0.05 for the pairwise comparison between the efavirenz group and the NRTI-sparing group, with no adjustment for multiple testing.

‡ P<0.05 for the pairwise comparison between the efavirenz group and the lopinavir–ritonavir group, with no adjustment for multiple testing.

§ P<0.05 for the pairwise comparison between the lopinavir–ritonavir group and the NRTI-sparing group, with no adjustment for multiple testing.

¶ Included in this category were aspartate aminotransferase, alanine aminotransferase, or both.

|| Included in this category were events of any grade reported by site investigators.

in the other two groups (P<0.01 for both comparisons), mainly because of more frequent elevations in fasting triglyceride levels.

#### RESISTANCE TO HIV DRUGS

HIV-1 drug-resistance mutations in protease or reverse transcriptase that were detected at the time of virologic failure are shown in Table 4. With the exclusion of minor protease mutations<sup>14</sup> and the assumption that no patients with missing genotyping data had resistance mutations, the

numbers of patients who had virologic failure and one or more drug-resistance mutations were 22 of 250 (9%) in the efavirenz group, 16 of 253 (6%) in the lopinavir–ritonavir group, and 39 of 250 (16%) in the NRTI-sparing group (P<0.05 for the comparison between the NRTI-sparing group and both the efavirenz group and the lopinavir–ritonavir group). Of the available genotypes from patients with virologic failure, 39 of 56 patients (70%) in the NRTI-sparing group had one or more drug-resistance mutations, as compared with 22 of 46

**Table 4. Summary of Resistance Mutations at the Time of Virologic Failure.\***

Variable	Efavirenz Group (N=250)		Lopinavir–Ritonavir Group (N=253)		NRTI-Sparing Group (N=250)	
	No. (%)	P Value vs. NRTI-Sparing Group	No. (%)	P Value vs. Efavirenz Group	No. (%)	P Value vs. Lopinavir–Ritonavir Group
Virologic-failure events	60 (24)		94 (37)		73 (29)	
Genotype available at virologic failure	46 (77)		78 (83)		56 (77)	
No sample available or HIV-1 RNA <500 copies/ml	8 (13)		7 (7)		10 (14)	
No sequence available (unable to amplify)	6 (10)		9 (10)		7 (10)	
Any mutation (excluding minor protease mutation)	22 (48)	0.03	16 (21)	0.002	39 (70)	<0.001
NRTI-associated mutation	14 (30)	0.02	15 (19)	0.19	6 (11)	0.23
M184V	8 (17)	0.01	13 (17)	1.00	1 (2)	<0.01
K65R	3 (7)	0.09	0	0.05	0	NA
Thymidine analogue–associated mutation†	2 (4)	1.0	1 (1)	0.56	2 (4)	0.57
NNRTI-associated mutation	20 (43)	0.03	2 (3)	<0.001	37 (66)	<0.001
K103N	11 (24)	0.002	0	<0.001	31 (55)	<0.001
Any protease mutation	39 (85)	0.61	61 (78)	0.48	45 (80)	0.83
Major protease mutation‡	0	0.50	0	NA	2 (4)	0.17
Mutation associated with two drug classes§	12 (26)	0.01	1 (1)	<0.001	4 (7)	0.16

\* Percentages of patients with mutations were calculated for those who had an available genotype at the time of virologic failure. Mutations that were evaluated included the following: NRTI: 41L, 44D, 62V, 65R, 69insert, 70R, 74V, 75I, 77L, 115F, 116Y, 118I, 151M, 184I/V, 210W, 215Y/F, and 219Q/E; non-nucleoside reverse-transcriptase inhibitor (NNRTI): 100I, 103N, 106 M/A, 108I, 181C, 188H/L/C, 190A/S, 225H, 230L, and 236L; and protease inhibitor: 10F/I/V/R, 13V, 16E, 20M/R/I, 24I, 30N, 32I, 33I/F/V, 35G, 36I/L/V, 43T, 46I/L, 47V/A, 48V, 50L/V, 53L, 54L/V/M/T/S/A, 58E, 60E, 62V, 63P, 69K, 71V/T/I/L, 73C/S/T/A, 77I, 82A/T/F/S/L, 84V, 85V, 88S/D, 90M, and 93L. NA denotes not applicable.

† Thymidine analogue–associated mutations 41L, 67N, 70R, 210W, 215Y/F, and 219Q/E were evaluated.

‡ Major protease mutations 30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, and 90M were evaluated.

§ Only major protease mutations were included in this category.

(48%) in the efavirenz group and 16 of 78 (21%) in the lopinavir–ritonavir group (for the NRTI-sparing group,  $P<0.001$  for the comparison with the lopinavir–ritonavir group and  $P=0.03$  for the comparison with the efavirenz group;  $P=0.002$  for the comparison between the lopinavir–ritonavir group and the efavirenz group).

Mutations that were associated with resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) (of which 71% were K103N) were more frequent in the NRTI-sparing group (66%) than in the efavirenz group (43%,  $P=0.03$ ). There was no significant difference between the lopinavir–ritonavir group and the efavirenz group in the frequency of the M184V mutation (associated with resistance to lamivudine) or those associated with thymidine analogue or any NRTI. Fewer patients

in the lopinavir–ritonavir group than in the efavirenz group had mutations associated with resistance to two drug classes (1% vs. 26%,  $P<0.001$ ) or the K65R substitution (0% vs. 7%,  $P=0.05$ ).

## DISCUSSION

In this 96-week, prospective, randomized comparison of potent regimens for initial therapy for patients with HIV-1 infection, virologic failure was less likely in the group receiving efavirenz plus two NRTIs than in the group receiving lopinavir–ritonavir plus two NRTIs. The NRTI-sparing regimen of lopinavir–ritonavir plus efavirenz had a virologic efficacy similar to that of efavirenz plus two NRTIs, but NNRTI resistance and lipid abnormalities, especially elevated triglycerides, were

more frequent. Clinically apparent lipoatrophy was reported infrequently. Recovery of limb fat favored the NRTI-sparing group. There was a trend toward a shorter time to regimen failure in the lopinavir–ritonavir group, as compared with the efavirenz group, but the difference was not significant after adjustment for multiple comparisons. The number of regimen-failure outcomes owing to adverse events was similar among the study groups, and there was no significant difference among the three groups in the time to treatment-limiting toxicity.

Patients who were receiving either of the regimens containing lopinavir–ritonavir had greater increases in the CD4 cell count than did those receiving efavirenz plus two NRTIs at week 96 but not at week 48. It has been suggested that HIV-1 protease inhibitors have antiapoptotic effects on CD4 cells that are independent of the antiviral effects.<sup>15</sup> However, it might be expected that a difference between the groups on the basis of this mechanism would be apparent earlier after initiation of treatment. A large, randomized strategy study showed no difference in the change in CD4 cell count for initial therapy with a protease inhibitor (mostly nelfinavir), as compared with an NNRTI-containing regimen.<sup>16</sup> In addition, the clinical significance of the differences in recovery in the CD4 cell count that we observed in our study is unclear.

Several factors may be associated with a better virologic response to one antiretroviral regimen over another, including greater potency, better tolerability, and higher rates of adherence. In this study, the regimen of efavirenz plus two NRTIs had greater overall virologic efficacy even when the analysis was restricted to patients with a high level of adherence, and the regimen appeared to suppress HIV-1 RNA levels more rapidly than the regimens containing lopinavir–ritonavir, although the clinical significance of this difference is not known (Fig. 2).

HIV-1 drug-resistance testing at the time of virologic failure revealed that NNRTI resistance occurred more frequently in the NRTI-sparing group than in the efavirenz group. This finding was not anticipated but may be explained, in part, by differences in the elimination half-lives of lopinavir–ritonavir and efavirenz. Although this hypothesis is speculative given the long half-life of efavirenz<sup>17</sup> and the relatively short half-life of

lopinavir–ritonavir, missed doses of lopinavir–ritonavir might result in periods with therapeutic levels of efavirenz but not lopinavir–ritonavir, resulting in the selection of NNRTI-resistant virus.

Previous studies have reported lower frequencies of NRTI resistance at the time of virologic failure among patients receiving lopinavir–ritonavir plus two NRTIs than among those receiving various other regimens.<sup>18,19</sup> However, in our study, among patients with virologic failure, the proportion of patients with any NRTI resistance mutation and specifically lamivudine resistance was similar in the lopinavir–ritonavir group and the efavirenz group. The presence of mutations associated with two drug classes, primarily M184V and K103N, was more common in the efavirenz group. The absence of major protease mutations in the lopinavir–ritonavir group was consistent with findings reported previously.<sup>19,20</sup>

The virologic efficacy of the nucleoside-sparing regimen of lopinavir–ritonavir plus efavirenz in our study clearly shows that NRTIs are not absolutely required for effective antiretroviral therapy. The increased frequency of lipid elevation and NNRTI resistance in the NRTI-sparing group should dampen enthusiasm for routine use of this regimen. However, the data support the use of combined therapy with lopinavir–ritonavir plus efavirenz in specific clinical situations in which options are limited, such as a contraindication for or an intolerance to NRTIs. The virologic efficacy of NRTI-sparing therapy with lopinavir–ritonavir and efavirenz supports the study of potent two-drug NRTI-sparing regimens for initial therapy.

Our study establishes the use of efavirenz plus two NRTIs as being more effective than lopinavir–ritonavir plus two NRTIs for initial therapy of HIV-1 infection, although the margin of superiority was moderate. Drug resistance was not a common outcome overall, but failure of efavirenz plus two NRTIs was often associated with NNRTI resistance, whereas failure of lopinavir–ritonavir plus two NRTIs was not associated with lopinavir resistance, and NRTI resistance was similar in the two groups. These results highlight the complexity of choosing initial therapy. Selection of initial therapy for an individual patient should take into consideration many factors, including virologic and immunologic response, tolerability,

short-term and long-term toxicity, and the resistance consequences associated with virologic failure.

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#### APPENDIX

In addition to the authors, the study team included the following members: P. Cain (Stanford University Medical Center), protocol field representative; M. Cooper, M. Dobson (Frontier Science and Technology Research Foundation), laboratory data coordinators; M. Dorosh (University of Colorado Health Sciences Center), community representative; P. Kondo (University of Hawaii), protocol laboratory technologist; D. Rusin (Frontier Science and Technology Research Foundation), data manager; K. Squires (Thomas Jefferson University), coinvestigator; P. Tran (Division of AIDS, National Institute of Allergy and Infectious Diseases), protocol pharmacist. The following were pharmaceutical representatives: S. Brun, R. Rode (Abbott Laboratories); M. Poblenz, M. Hitchcock (Gilead Sciences).

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