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## Comparison of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection

Gregory K. Robbins, M.D., M.P.H., Victor De Gruttola, Sc.D., Robert W. Shafer, M.D., Laura M. Smeaton, M.S., Sally W. Snyder, B.S., Carla Pettinelli, M.D., Ph.D., Michael P. Dubé, M.D., Margaret A. Fischl, M.D., Richard B. Pollard, M.D., Robert Delapenha, M.D., Linda Gedeon, B.S., Charles van der Horst, M.D., Robert L. Murphy, M.D., Mark I. Becker, Pharm.D., Richard T. D'Aquila, M.D., Stefano Vella, M.D., Thomas C. Merigan, M.D., and Martin S. Hirsch, M.D., for the AIDS Clinical Trials Group 384 Team\*

### ABSTRACT

#### BACKGROUND

The optimal sequencing of antiretroviral regimens for the treatment of infection with human immunodeficiency virus type 1 (HIV-1) is unknown. We compared several different antiretroviral treatment strategies.

#### METHODS

This multicenter, randomized, partially double-blind trial used a factorial design to compare pairs of sequential three-drug regimens, starting with a regimen including zidovudine and lamivudine or a regimen including didanosine and stavudine in combination with either nelfinavir or efavirenz. The primary end point was the length of time to the failure of the second three-drug regimen.

#### RESULTS

A total of 620 subjects who had not previously received antiretroviral therapy were followed for a median of 2.3 years. Starting with a three-drug regimen containing efavirenz combined with zidovudine and lamivudine (but not efavirenz combined with didanosine and stavudine) appeared to delay the failure of the second regimen, as compared with starting with a regimen containing nelfinavir (hazard ratio for failure of the second regimen, 0.71; 95 percent confidence interval, 0.48 to 1.06), as well as to delay the second virologic failure (hazard ratio, 0.56; 95 percent confidence interval, 0.29 to 1.09), and significantly delayed the failure of the first regimen (hazard ratio, 0.39) and the first virologic failure (hazard ratio, 0.34). Starting with zidovudine and lamivudine combined with efavirenz (but not zidovudine and lamivudine combined with nelfinavir) appeared to delay the failure of the second regimen, as compared with starting with didanosine and stavudine (hazard ratio, 0.68), and significantly delayed both the first and the second virologic failures (hazard ratio for the first virologic failure, 0.39; hazard ratio for the second virologic failure, 0.47), as well as the failure of the first regimen (hazard ratio, 0.35). The initial use of zidovudine, lamivudine, and efavirenz resulted in a shorter time to viral suppression.

#### CONCLUSIONS

The efficacy of antiretroviral drugs depends on how they are combined. The combination of zidovudine, lamivudine, and efavirenz is superior to the other antiretroviral regimens used as initial therapy in this study.

From Harvard Medical School (G.K.R., M.S.H.) and the Harvard School of Public Health (V.D.G., L.M.S.) — both in Boston; the Stanford University Medical Center, Stanford, Calif. (R.W.S., T.C.M.); Social & Scientific Systems, Silver Spring, Md. (S.W.S.); the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. (C.P.); the Indiana University School of Medicine, Indianapolis (M.P.D.); the University of Miami School of Medicine, Miami (M.A.F.); the University of California–Davis Medical Center, Sacramento (R.B.P.); Howard University, Washington, D.C. (R.D.); Frontier Science & Technology Research Foundation, Amherst, N.Y. (L.G.); the University of North Carolina School of Medicine, Chapel Hill (C.H.); Northwestern University, Chicago (R.L.M.); Agouron Pharmaceuticals, La Jolla, Calif. (M.I.B.); the Vanderbilt University Medical Center, Nashville (R.T.D.); and the Istituto Superiore di Sanita, Rome (S.V). Address reprint requests to Dr. Robbins at Massachusetts General Hospital, Infectious Disease Unit, 55 Fruit St., Boston, MA 02114, or at grobbins@partners.org.

\*Other members of the AIDS Clinical Trials Group (ACTG) 384 Team are listed in the Appendix.

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THESE ARE MANY OPTIONS FOR THE initiation of antiretroviral therapy for infection with human immunodeficiency virus type 1 (HIV-1), the cause of the acquired immunodeficiency syndrome (AIDS).<sup>1-3</sup> The current standard of care is to use two nucleoside reverse-transcriptase inhibitors (nucleoside analogues) plus a third agent from another class. Regimens should be well tolerated, provide durable viral suppression, and preserve future treatment options. The optimal sequencing of antiretroviral regimens for HIV-1 infection is unknown. We conducted a trial to compare treatment strategies using different combinations and different sequences of antiretroviral drugs designed to achieve these goals.

## METHODS

### STUDY DESIGN

The AIDS Clinical Trials Group (ACTG) study 384 was a multicenter trial conducted in the United States and Italy that randomly assigned subjects to six treatment groups. The trial had three primary objectives: to compare the initiation of therapy with an antiretroviral regimen including efavirenz with initiation with a regimen including nelfinavir (both in combination with two nucleoside reverse-transcriptase inhibitors); to compare the initiation of therapy with an antiretroviral regimen including zidovudine and lamivudine with initiation with a regimen including stavudine and didanosine (in combination with either nelfinavir or efavirenz); and to compare the use of a four-drug regimen including two nucleoside analogues, efavirenz, and nelfinavir with the use of two sequential three-drug regimens.

The trial used a two-by-three factorial design (Fig. 1). The first comparison (factor) was of the order in which the combinations of nucleoside analogues were administered: didanosine and stavudine followed by zidovudine and lamivudine versus zidovudine and lamivudine followed by didanosine and stavudine. The second comparison (factor) was of the drugs that were combined with the nucleoside analogues: nelfinavir followed by efavirenz versus efavirenz followed by nelfinavir versus simultaneous efavirenz and nelfinavir. Four groups received two consecutive three-drug regimens; two groups received single four-drug regimens. Here we focus on comparisons among the three-drug regimens; the results of the comparison between the four-drug regimens and the sequential three-day regimens are

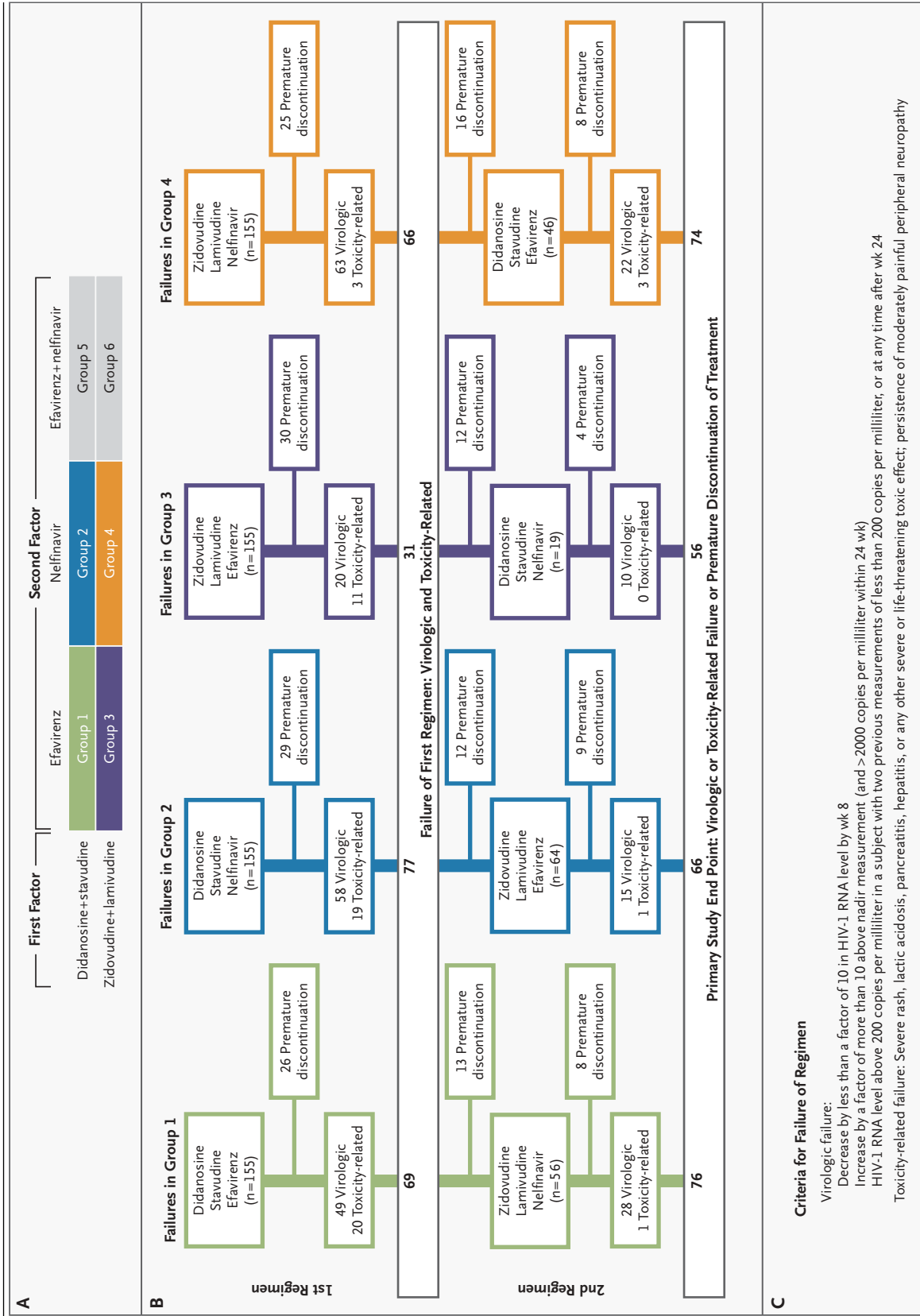
### Figure 1 (facing page). Study Design and Disposition of Subjects.

Panel A shows the factorial design of the trial and the initial treatment regimens for each of the six groups. The first treatment factor was the choice of the combination of two nucleoside analogues, and the second treatment factor was the choice of efavirenz, nelfinavir, or both. Subjects in groups 1, 2, 3, and 4 who had a treatment failure were switched to a new complementary regimen (Panel B). The discontinuation of use of the study medications for any reason was counted as a primary study end point but was not considered in the analysis of the time to the failure of the first regimen. After the failure of the second regimen, subjects were offered a choice of salvage regimens. The criteria for the failure of study regimens are shown in Panel C. Measurements of HIV-1 RNA that met the criteria for virologic failure were confirmed by means of a second test performed within two to six weeks after the first test. Toxic effects were graded according to the classification system of the Division of AIDS.<sup>4</sup> The substitution of stavudine for zidovudine or lamivudine for didanosine for reasons of toxic effects or intolerance was permitted. Dose reduction for reasons of toxic effects or intolerance was permitted for zidovudine, stavudine, and didanosine (in accordance with drug-prescribing information).

presented by Shafer et al. elsewhere in this issue of the Journal.<sup>5</sup>

Two substitutions of antiretroviral drugs (stavudine for zidovudine or lamivudine for didanosine) were permitted for reasons of drug intolerance without the regimen's being considered to have failed. Regimen failures were defined according to either virologic or toxicity-related criteria (Fig. 1C). After a confirmed failure, subjects in the three-drug-regimen groups began receiving their second three-drug regimen, which was chosen in such a way as to minimize cross-resistance and toxicity through the use of new antiretroviral drugs with different resistance and toxicity profiles. The primary end point was the time to the failure of the second of the consecutive three-drug regimens, regardless of the reason for the failure (virologic failure or toxic effects), or the permanent discontinuation of use of all study medications for any reason.

Secondary end points included the time to the failure of the first three-drug regimen, the times to the first and second virologic failures (regardless of whether the subject was receiving study medications at the time), changes from base line in the CD4 cell count (measured at weeks 48, 96, and 144), and toxic effects. End points that were defined after the



completion of the primary analysis included the time to initial viral suppression, as well as the occurrence of virologic failure with genotypic resistance to the three different classes of antiretroviral drugs (nucleoside analogues, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors); results for the latter are presented by Shafer et al.<sup>5</sup>

#### STUDY SUBJECTS

Subjects were eligible if they had a plasma HIV-1 RNA level of at least 500 copies per milliliter, had previously received antiretroviral therapy for fewer than 7 days, and had not had any clinically significant laboratory abnormalities or serious acute illnesses within the 14 days before study entry.<sup>6</sup> Subjects were recruited from 58 sites in the United States and 23 sites in Italy.

#### STUDY TREATMENTS

Nucleoside analogues were provided on an open-label basis. Didanosine was administered at a dose of 400 mg daily (250 mg daily if the patient weighed less than 60 kg; enteric-coated tablets were available on request during the final calendar year of the study); stavudine was given at a dose of 40 mg twice daily (30 mg twice daily if the patient weighed less than 60 kg); and lamivudine (150 mg) and zidovudine (300 mg) were administered as a fixed-dose combination twice daily. Efavirenz and nelfinavir were administered in a double-blind manner with matching placebos: efavirenz (600 mg) or matching placebo was given nightly, and nelfinavir (1250 mg) or matching placebo was given twice daily.

#### ENROLLMENT AND MONITORING

Subjects were enrolled between October 1998 and November 1999. Clinical assessments and plasma HIV-1 RNA measurements were obtained at screening, at entry, at weeks 4, 8, 12, 16, 20, and 24, and every eight weeks thereafter. CD4 cell counts and laboratory measurements of safety-related variables were also performed at regular intervals,<sup>6</sup> and adherence was self-reported<sup>7</sup> and health-status questionnaires were completed at selected visits. HIV-1 RNA levels were measured with the use of an HIV polymerase-chain-reaction assay (Roche Ultrasensitive Amplicor assay, version 1.0) with a lower limit of detection of 50 copies per milliliter at a central laboratory in each country.

The protocol was approved by the local institutional review boards. Written informed consent was obtained from all subjects. There were three planned

interim analyses of efficacy and safety by an independent data and safety monitoring board, which used the Haybittle–Peto stopping boundaries for sequential monitoring.<sup>8</sup>

#### SAMPLE SIZE AND RANDOMIZATION

The study was designed to enroll 800 subjects in the six study groups in a ratio of 5:5:5:5:6:6. Under the assumption of an exponential model of time to failure adjusted for uniform accrual over a one-year period and subsequent follow-up of two years, this original sample size provided the study with 85 percent power to detect a hazard ratio for the failure of the second regimen of 1.57 between the initiation of therapy with a regimen including efavirenz and initiation with a regimen including nelfinavir and between initiation with zidovudine–lamivudine and initiation with stavudine–didanosine.<sup>6</sup> Central randomization was performed with the use of a permuted-block computer algorithm with two stratification factors: the HIV-1 RNA level at screening ( $<4.0 \log_{10}$  copies per milliliter,  $4.0 \log_{10}$  to  $5.0 \log_{10}$  copies per milliliter, and  $>5.0 \log_{10}$  copies per milliliter) and the country. Additional details about the study are available elsewhere.<sup>6</sup>

#### STATISTICAL ANALYSIS

Survival functions for the time-to-event end points were estimated according to the method of Kaplan and Meier.<sup>9</sup> Cox proportional-hazards models that included the treatment factors (initiation with efavirenz vs. nelfinavir and initiation with zidovudine–lamivudine vs. stavudine–didanosine), HIV-1 RNA strata, and all two-way and three-way interactions were used to analyze each end point. When a significant interaction was found for an end point (as assessed with the use of a Wald test<sup>10</sup>), analyses were performed separately for individual treatment groups as described below rather than pooling among groups. Confidence intervals were calculated at 97.5 percent according to the Bonferroni method and are reported as adjusted 95 percent confidence intervals.<sup>11</sup>

Specifically, each primary objective involved two pairwise comparisons (and therefore adjustment to a significance level of 0.025): a comparison between the group that initially received didanosine, stavudine, and efavirenz (group 1) and the group that initially received didanosine, stavudine, and nelfinavir (group 2) and a comparison between the group that initially received zidovudine, lamivudine, and efavirenz (group 3) and the group that initially received

zidovudine, lamivudine, and nelfinavir (group 4) for the comparison of efavirenz and nelfinavir; and a comparison between group 1 and group 3 and a comparison between group 2 and group 4 for the comparison of zidovudine–lamivudine and stavudine–didanosine.

For end points for which there were no significant statistical interactions, the pooled comparisons were stratified according to treatment factor in addition to both of the stratification factors used for randomization. The study objectives were investigated with the use of stratified Mantel–Haenszel log-rank tests; estimates of hazard ratios and associated confidence intervals were obtained with the use of Cox proportional-hazard models.<sup>12</sup>

Data were collected on serious toxic effects (grade 3 or worse and toxic effects resulting in the modification of doses). Because of specific concerns about toxicity, rash, peripheral neuropathy, other neurologic abnormalities, and pancreatitis were also reported if they were mild to moderate.<sup>13,14</sup> The primary safety end point was the length of time to the first serious toxic effect. Comparisons of the rates of toxic effects were made according to the initial regimen. Toxic effects that occurred after a new study regimen was begun or more than eight weeks after treatment with all study medications was discontinued were excluded. For comparisons in which there were significant differences among the randomized study groups, post hoc comparisons were performed by pooling across appropriate groups. Self-reported adherence was summarized as the percentage of the prescribed regimen taken during the scheduled sampling periods (4 days before each scheduled study visit) within the first 32 weeks of study treatment.

RESULTS

**BASE-LINE CHARACTERISTICS OF THE SUBJECTS**

Overall, 987 subjects were enrolled; 7 never received study medications and were excluded from all analyses. A total of 620 subjects were enrolled in groups 1, 2, 3, and 4 (568 in the United States and 52 in Italy). Five of these subjects reported having received some previous antiretroviral therapy. The median base-line plasma HIV-1 RNA level was 4.9 log<sub>10</sub> copies per milliliter. Subjects were stratified according to screening HIV-1 RNA values: 17 percent of the subjects had levels below 4.0 log<sub>10</sub> copies per milliliter, 42 percent had levels between 4.0 and 5.0 log<sub>10</sub> copies per milliliter, and 41 percent had

levels above 5.0 log<sub>10</sub> copies per milliliter. The median CD4 cell count was 280 per cubic millimeter; 24 percent of the subjects had counts below 100 per cubic millimeter. Base-line characteristics were similar among the four groups (Table 1).

**STUDY FOLLOW-UP AND ADHERENCE**

The median study follow-up among the four groups was 28 months, with a median duration of study treatment (including study-supplied salvage regimens) of 27 months. There were six deaths, and 20 subjects had new AIDS-defining illnesses. In 16 subjects, stavudine was substituted for zidovudine, and in 50 subjects, lamivudine was substituted for didanosine. There were no significant differences among the groups in the length of time to the discontinuation of study treatment. The mean rate of self-reported adherence among patients receiving study medications ranged from 97.6 percent to 98.2 percent, with no significant differences among groups.

**Table 1. Base-Line Characteristics of the Subjects.\***

Characteristic	All Groups Receiving 2 Sequential 3-Drug Regimens				
	All Groups (N=620)	Group 1 (N=155)	Group 2 (N=155)	Group 3 (N=155)	Group 4 (N=155)
Age (yr)					
Median	36	35	35	36	34
Interquartile range	30–42	29–41	30–41	30–44	29–40
Male sex (%)	81	85	81	82	75
Race or ethnic group (%)					
Non-Hispanic white	46	47	50	48	38
Non-Hispanic black	35	37	31	33	38
Hispanic	17	13	17	17	23
Asian	2	3	1	2	1
Native American	<1	0	1	0	0
Intravenous drug use (%)†	9	7	10	11	7
CD4 cell count (per mm <sup>3</sup> )					
Median	280	273	264	272	307
Interquartile range	105–454	66–451	100–440	88–466	161–462
Plasma HIV-1 RNA level (log <sub>10</sub> copies/ml)					
Median	4.9	5.0	5.0	4.9	4.9
Interquartile range	4.3–5.5	4.3–5.5	4.3–5.6	4.3–5.4	4.2–5.4

\* Group 1 initially received didanosine, stavudine, and efavirenz; group 2 initially received didanosine, stavudine, and nelfinavir; group 3 initially received zidovudine, lamivudine, and efavirenz; and group 4 initially received zidovudine, lamivudine, and nelfinavir. Percentages may not add to 100 because of rounding.  
 † Data are for subjects who reported ever having used intravenous drugs.

**PRIMARY END POINT**

The primary study end point was reached in 272 subjects (44 percent) (Fig. 1). Eighty subjects had two regimen failures, and 192 prematurely discontinued study treatment. Of the discontinuations, 82 occurred after a virologic or toxicity-related failure of the first regimen. Of the remaining 110 subjects in whom the primary study end point was reached, 40 were lost to follow-up; 36 chose to discontinue study treatment; 19 were required to discontinue treatment because of coexisting conditions or the use of prohibited medications; 8 had low-grade toxic effects; 4 were required to discontinue treatment because of pregnancy; and 3 died.

For the primary end point, there was a significant interaction between the two treatment factors — the initial combination of two nucleoside analogues and the initiation of treatment with efavirenz rather than nelfinavir ( $P=0.02$ ). The two pairwise comparisons for each primary end point showed a trend that favored the initiation of treatment with efavirenz over the initiation with nelfinavir when zidovudine and lamivudine were used as the nucleoside analogues (hazard ratio for the failure of the second regimen, 0.71; 95 percent confidence interval, 0.48 to 1.06) but not when didanosine and stavudine were used (Fig. 2 and 3A). Similarly, there was a trend favoring the initiation of therapy with zidovudine and lamivudine when efavirenz was used (hazard ratio, 0.68; 95 percent confidence interval, 0.46 to 1.01) but not when nelfinavir was used (Fig. 2 and 3A). There was a nearly significant interaction among the treatment factors and the HIV-1 RNA stratum ( $P=0.06$ ). In subgroup analyses according to HIV-1 RNA stratum, the trend favoring the combination of zidovudine, lamivudine, and efavirenz over zidovudine, lamivudine, and nelfinavir was present even in the highest stratum (hazard ratio, 0.48; 95 percent confidence interval, 0.23 to 1.01), as was the trend favoring zidovudine, lamivudine, and efavirenz over didanosine, stavudine, and efavirenz (hazard ratio, 0.48; 95 percent confidence interval, 0.23 to 1.02).

**SECONDARY END POINTS**

Of the subjects in whom the primary end point was reached, 27 percent had no further follow-up, 47 percent had at least 6 months of follow-up for the secondary end points, and 34 percent had at least 12 months of such follow-up. Overall, 114 subjects (18 percent; 38 subjects in group 1, 26 in group 2, 18 in group 3, and 32 in group 4) had two succes-

sive virologic failures, and 33 of these second virologic failures occurred after the primary end point was reached. The interaction between the two treatment factors with respect to the occurrence of two virologic failures was significant ( $P=0.004$ ). There was a trend favoring the initiation of therapy with efavirenz over initiation with nelfinavir when zidovudine and lamivudine were used (hazard ratio for two virologic failures, 0.56; 95 percent confidence interval, 0.29 to 1.09), and there was a significant advantage of initiation with zidovudine, lamivudine, and efavirenz over initiation with stavudine, didanosine, and efavirenz (hazard ratio, 0.47; 95 percent confidence interval, 0.24 to 0.89) (Fig. 2 and 3B). There was also a trend favoring initiation with nelfinavir, didanosine, and stavudine over initiation with efavirenz, didanosine, and stavudine (hazard ratio, 1.70; 95 percent confidence interval, 0.95 to 3.05). This benefit appears to result mostly from the second antiretroviral regimen of zidovudine, lamivudine, and efavirenz (group 2) because there were no differences in the time to the failure of the first regimens. In this analysis, all the effects were qualitatively similar to, and generally stronger than, the effects on the primary end point (Fig. 2 and 3B).

Analyses of other secondary end points also suggest that the results for the primary end point were driven by the benefit of initiation with efavirenz, zidovudine, and lamivudine. Of the 243 failures of the first regimen, 190 were virologic failures, and 53 were toxicity-related. Among the subjects in whom the first 235 first virologic failures occurred, 46 had their first virologic failure after the discontinuation of treatment with the first regimen. All the effects were similar to those on the primary end point ( $P=0.002$  for the effect of the interaction between the treatment factors on the hazard of failure of the first regimen, and  $P<0.001$  for the effect of the interaction between these factors on the hazard of first virologic failure). The benefits of initiation with efavirenz rather than nelfinavir when zidovudine and lamivudine were used were significant for these two end points (hazard ratio for the failure of the first regimen, 0.39; 95 percent confidence interval, 0.24 to 0.64; hazard ratio for the first virologic failure, 0.34; 95 percent confidence interval, 0.21 to 0.56) (Fig. 2, 3C, and 3D). Post hoc analysis of these end points after adjustment for all six possible pairwise comparisons among the treatment groups showed that the combination of efavirenz, zidovudine, and lamivudine was superior to all other three-drug regimens used as initial treatment in this study.

There were differences among the groups in the time to the first measurement of plasma HIV-1 RNA of less than 50 copies per milliliter ( $P < 0.001$  for the four-way comparison by the log-rank test), and there was an interaction of borderline significance between the treatment factors ( $P = 0.05$ ). The initiation of therapy with a regimen containing efavirenz led to faster viral suppression than initiation with nelfinavir ( $P < 0.001$ ) (see Supplementary Appendix 1, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). For the time to viral suppression, there was a trend favoring regimens containing zidovudine and lamivudine over regimens containing didanosine and stavudine ( $P = 0.09$ ).

**CD4 CELL COUNTS**

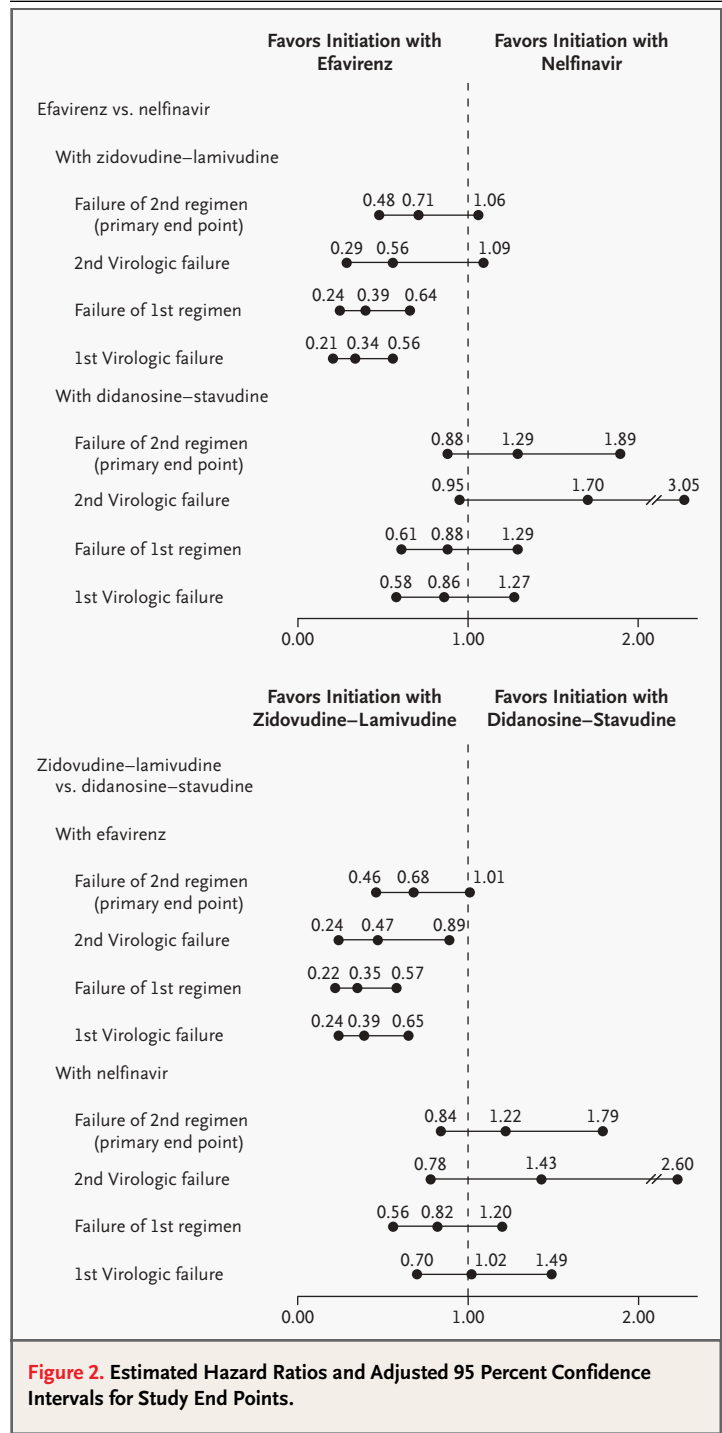
CD4 cell counts increased from base line by a median of 166 cells per cubic millimeter by week 48 (according to data on 514 subjects), by a median of +242 cells per cubic millimeter by week 96 (in 459 subjects), and by a median of 285 cells per cubic millimeter by week 144 (in 257 subjects). There were no significant differences in the CD4 cell count according to group or treatment factor (data not shown).

**TOXIC EFFECTS**

There was a significant difference among the four groups in the time to the first serious toxic effect (an effect of grade 3 or worse or necessitating a modification of the regimen or the dose;  $P < 0.001$  for the four-way comparison) (Fig. 4A). Since the curves for the time to the first serious toxic effect with regimens containing didanosine and stavudine diverged from the curves associated with regimens containing zidovudine and lamivudine after week 24, we performed post hoc analyses according to this factor. The initial use of regimens containing zidovudine and lamivudine delayed the occurrence of the first serious toxic effect, as compared with regimens containing didanosine and stavudine ( $P < 0.001$ ) (Fig. 4B) and delayed the occurrence of the first symptom or diagnosis of peripheral neuropathy ( $P < 0.001$ ) (Fig. 4D).

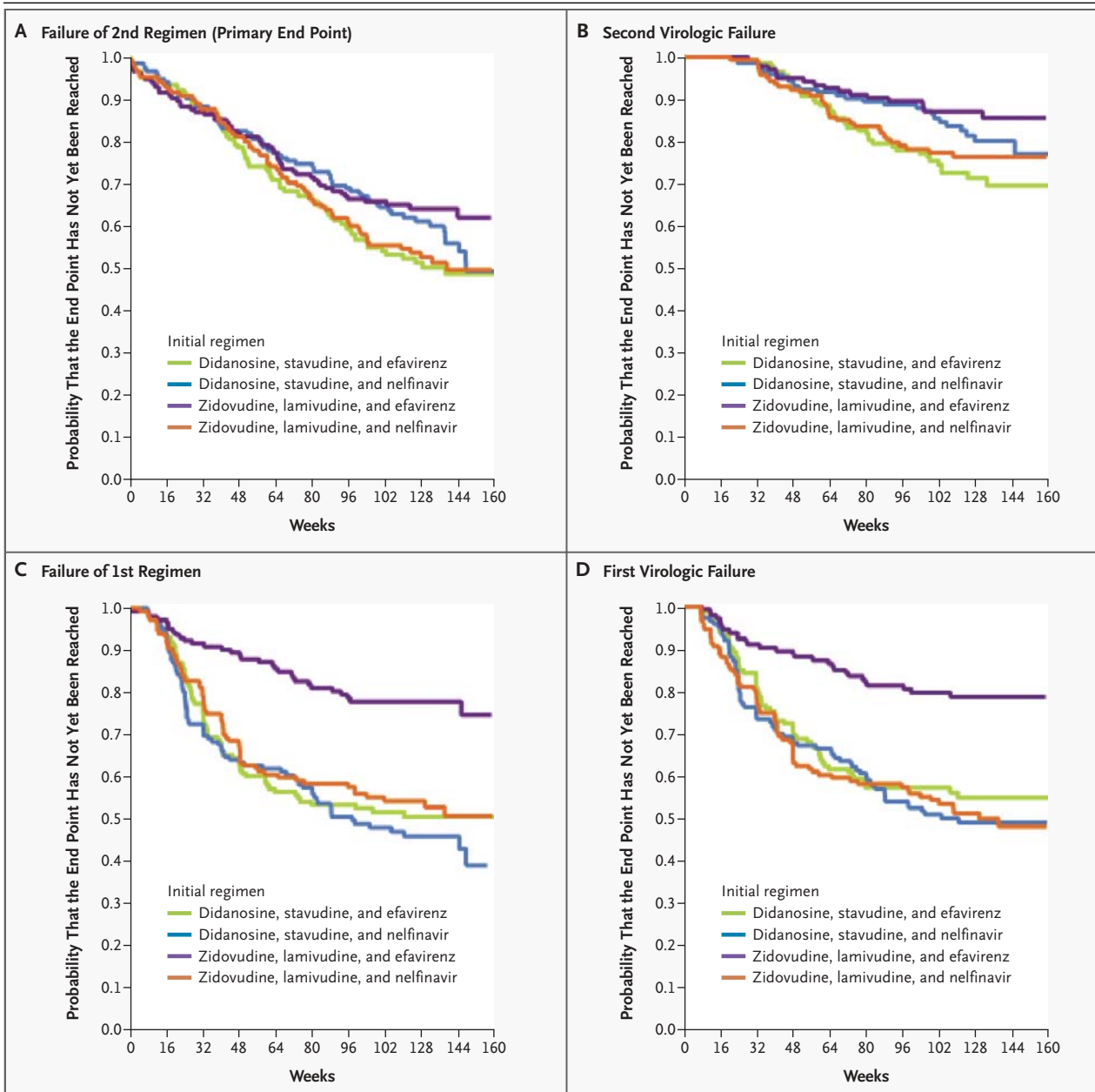
**DISCUSSION**

Our randomized trial addressed the question of how to initiate antiretroviral therapy in HIV-1-infected persons and evaluated two different combinations of nucleoside analogues given with either the non-nucleoside reverse-transcriptase inhibitor efavirenz



**Figure 2. Estimated Hazard Ratios and Adjusted 95 Percent Confidence Intervals for Study End Points.**

or the protease inhibitor nelfinavir. Several initial regimens have been proposed on the basis of previous studies.<sup>1,3,15,16</sup> Many trials have used as their primary end point viral suppression 24 to 48 weeks after the initiation of therapy and have not followed

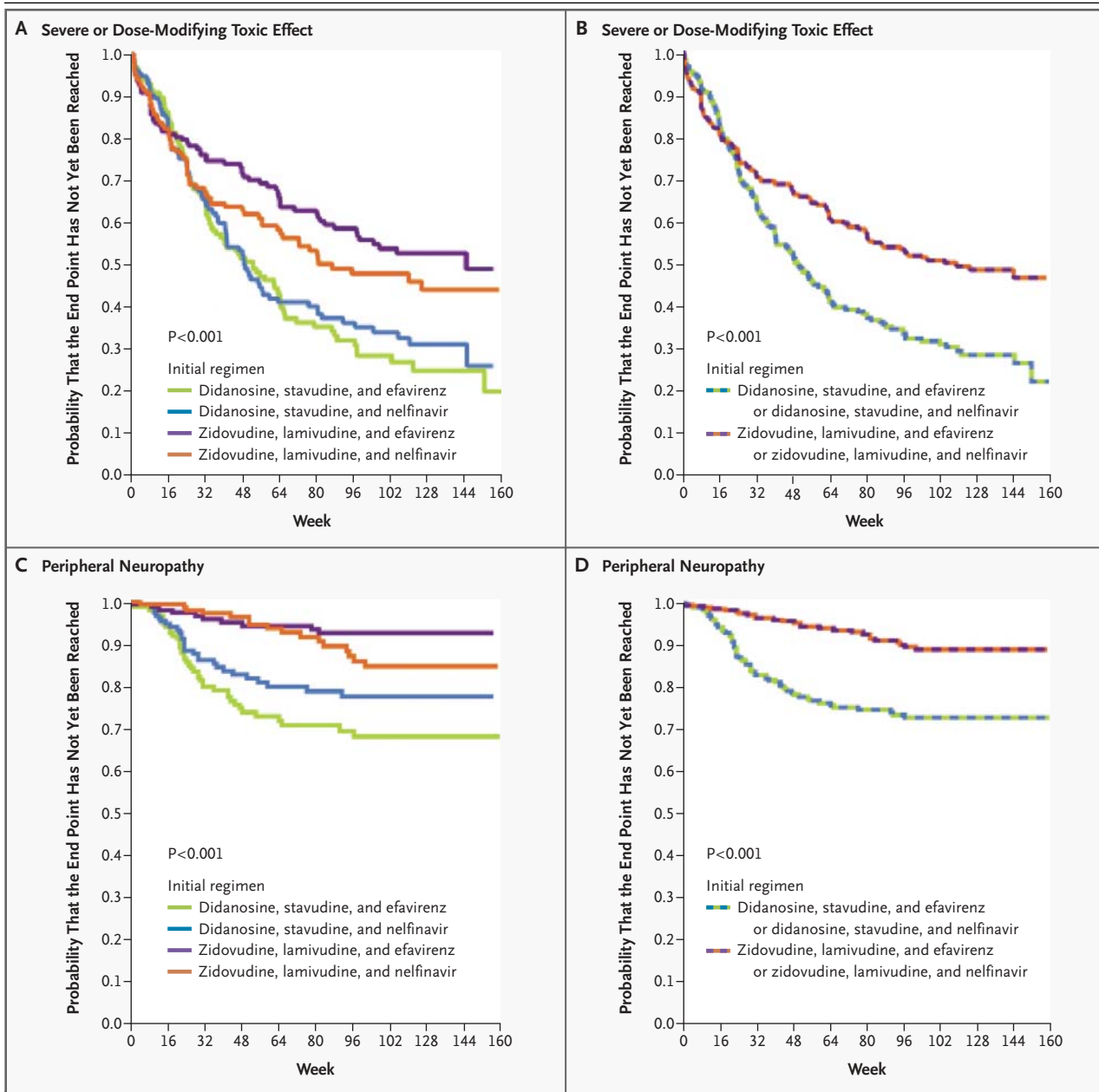


**Figure 3.** Kaplan–Meier Curves Showing Estimated Time to the Primary Study End Point (Failure of the Second Regimen, Panel A), the Second Virologic Failure (Panel B), the Failure of the First Regimen (Panel C), and the First Virologic Failure (Panel D).

subjects for responses to subsequent regimens. Our study was designed to provide a minimum of two years of follow-up, and the primary end point was the failure of two successive regimens, as a result of inadequate viral suppression or toxic effects, or the premature discontinuation of study medications. This end point was chosen for the comparison of different strategies for the sequencing of antiretroviral drugs because it reflects the clinical goal of

retaining patients in follow-up and keeping them under continuous treatment with tolerable and effective antiretroviral regimens. Secondary analyses included those of the failure of the initial regimen as assessed on the basis of virologic or toxicity-related criteria; the first and second virologic failures irrespective of treatment status; and the time to viral suppression.

A major finding was the significant effect on the



**Figure 4.** Kaplan–Meier Curves Showing the Time to the First Severe Toxic Effect or Toxic Effect Resulting in Modification of the Dose According to Regimen (Panel A) and According to Nucleoside Analogues Used (Panel B) and the Time to Peripheral Neuropathy According to Regimen (Panel C) and According to Nucleoside Analogues Used (Panel D).

Peripheral neuropathy was defined by clinical diagnosis or the occurrence of the first moderate sign or symptom (grade  $\geq 3$ ).

rate of the primary end point — the failure of two consecutive three-drug regimens — of the interaction between the combination of nucleoside analogues and the use of efavirenz or nelfinavir: strong trends favored the initiation of therapy with zidovudine, lamivudine, and efavirenz over the initiation of therapy with other regimens (groups 1 and 4).

Group 2 was not included in this comparison, since it received the same regimens in reverse order. The trends favoring group 3 were further supported by significant differences among the groups in the times to the failure of the first regimen and the first virologic failure, trends and significant differences among the groups in the time to the second virolog-

ic failure, and the post hoc analysis of the time to viral suppression. Also noteworthy is the nearly significant effect on the rate of the primary study end point of the interaction among the treatment factors and the HIV-1 RNA stratum, which implies that even among the subjects who had high viral loads at screening (HIV-1 RNA level,  $>5.0 \log_{10}$  copies per milliliter) the combination of zidovudine, lamivudine, and efavirenz was more effective than the other regimens with which it was compared (groups 1 and 4).

The consistency of the results among different end points shows that our primary findings do not depend on the way in which treatment discontinuation was handled in our analyses. An analysis of an end point whose definition encompasses discontinuation of therapy for any reason can result in estimates of treatment effects that are biased toward attenuation if losses to follow-up are actually unrelated to treatment. Because the rates of premature discontinuation were similar among treatment groups, it is not surprising that the effects of therapy were greatest for end points that did not include discontinuation of study treatment in their definition.

Subjects who initially received didanosine and stavudine had substantially more toxic effects than those who initially received zidovudine and lamivudine, particularly with respect to peripheral neuropathy. Given these results and those of earlier suggestive studies,<sup>12,13</sup> the combination of didanosine and stavudine should probably no longer be considered for use as part of an initial antiretroviral regimen. Since the risk of a first serious toxic effect decreased over time in the groups that initially received didanosine and stavudine,<sup>5</sup> the implications are less clear for persons who are currently tolerating this combination and have satisfactory viral suppression.

Although the mechanisms underlying the favorable interactions among zidovudine, lamivudine, and efavirenz are still being explored, this combination provided greater antiretroviral potency than the other combinations tested and resulted in a lower rate of failure with genotypic resistance to each class of anti-HIV drugs.<sup>5</sup> Perhaps most important, toxic effects occurred less commonly in subjects who initially received zidovudine and lamivudine. It is possible that minor toxic effects or intolerance may have reduced the level of adherence to, and therefore the effectiveness of, certain regimens, without resulting in the permanent discontinuation of treatment. However, our initial analyses of adherence have not shown a significant difference among groups. Self-reported adherence for the four days preceding se-

lected study visits was very high and may represent an overestimate of actual adherence. More detailed analyses of the levels of antiretroviral drugs, pharmacokinetic interactions, adherence, resistance, and immunology are under way.

In summary, our study demonstrated a strong interaction between the choice of a combination of two nucleoside analogues and the choice of efavirenz or nelfinavir. The initiation of therapy with zidovudine, lamivudine, and efavirenz was the optimal strategy. These findings might have been different had alternative three-drug combinations been used, and they cannot be extrapolated to regimens including other drugs from the same classes. Investigations of the optimal use of other combinations of drugs may also benefit from the assessment of their interactions by means of factorial study designs. Our results demonstrate the benefit of the combination of zidovudine, lamivudine, and efavirenz over the other three-drug combinations we studied. Furthermore, this benefit was apparent even within the subgroup of subjects who had HIV-1 RNA levels above  $5.0 \log_{10}$  copies per milliliter at screening. The results of this and other studies<sup>16</sup> indicate that the combination of zidovudine, lamivudine, and efavirenz is a particularly useful regimen for the initiation of therapy in HIV-1-infected persons who have not previously been treated and could serve as the standard against which new regimens are compared. The results and conclusions of this study have been incorporated into the recently released HIV-treatment guidelines of the Department of Health and Human Services.<sup>2</sup>

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APPENDIX

Other members of the ACTG 384 team were M. Nokta (University of Texas, Galveston), V. Johnson (University of Alabama, Birmingham), G. Morse (State University of New York, Buffalo), B. Putnam (University of Colorado), M. Klebert (Washington University), A. Martinez (National Institutes of Health), A. Chiesi, C. Tomino (Istituto Superiore de Sanita), S. Deeks (University of California, San Francisco), M. Testa (Harvard School of Public Health), T. Nevin (Social & Scientific Systems), J. Levin, V. French, O. Fennell (Adult AIDS Clinical Trials Group Community Constituency Group), M. Stevens, R. Grosso, B. Dusak, I. Matozzo, I. Frank, K. Maffei, D. Kim (University of Pennsylvania), S. Marrero, O. Mendez, I. Torres, N. Rabell (University of Puerto Rico), G. Casey, C. Derkowski (University of Texas, Galveston), C. Fietzer, R. Nelson, K. Fox, R. Sanders (University of Minnesota), W. Wallace (University of Iowa), S. Swindells (University of Nebraska), H. Rominger, J. Richardson (Indiana University Hospital), P. Tebas, D. DeMarco, M. Royal (Washington University), B. Berzins (Northwestern University), H. Kessler (Rush-Presbyterian-St. Luke's Medical Center), J. Forcht, D. Tolenaar, C. Talabucon, C. Gonzalez (New York University/Bellevue), S. Wright, J. Graham (University of Alabama, Birmingham), C. Basler, S. Canmann (University of Colorado Health Sciences Center), P. Cain, S. Stoudt, J. Norris, S. Valle (Stanford University), S. Tedder, C. Hamilton (Duke University Medical Center), T. Flynn, K. Hartman (Massachusetts General Hospital), H. Fitch (Beth Israel Deaconess Medical Center), T. Cooley (Boston Medical Center and Harvard University), J. Frederick, S. Souza (University of Hawaii), D. Baker, A. Weiss, B. Becker, I. Wiggins (Johns Hopkins University), R. Reichman, M. Shoemaker, R. Hewitt, T. O'Hara (University of Rochester Medical Center), J. Lertora, R. Clark, M. Beilke, J. Dumestre (Tulane University), A. Moe, M. Witt, M. Guerrero, T. Maldonado (University of California, Los Angeles), A. Collier, B. Royer, J. Stekler, J. Conley (University of Washington), M. Dolan, E. Chusid, H. Sacks, I. Lowy (Mt. Sinai Medical Center), M. Jacobson, J. Volinski (San Francisco General Hospital), T. Stroberg, R. Gulick, M. Glesby, V. Hughes (Cornell University), R. Arcieri, M. Pirillo, C. Galluzzo, E. Germinario, R. Amici, M. Marzi, A. Nobile, R. Di Nallo, C. Polizzi (Istituto Superiore di Sanita), O. Coronado, G. Fasulo (Ospedale Maggiore), G. Carosi, F. Castelli (Università degli Studi di Brescia, Spedali Civili di Brescia), M. Di Pietro, F. Vichi (Ospedale Santa Maria Annunziata), G. Sterrantino, S. Ambu (Azienda Ospedaliera Careggi), M. Cargnel, P. Meraviglia, F. Niero, A. Capetti, A. D'Arminio Monforte, S. Sollima, C. Balotta (Ospedale Luigi Sacco), S. Delia, M. Ciardi, G. d'Ettore, G. Forcina (Università degli Studi di Roma La Sapienza, Policlinico Umberto I), M. Soranzo, A. Macor (Ospedale Amadeo Di Savoia), D. Bassetti, A. Di Biagio (Università de Genova), L. Minoli, R. Maserati (Istituto di Recupero e Cura a Carattere Scientifico Policlinico S. Matteo), F. Ghinelli, L. Sighinolfi (Azienda Arcispedale Sant' Anna), A. Riva, G. Scalise (Università degli Studi di Ancona Ospedale Umberto I), D. Santoro, E. Rinaldi (Ospedale Sant' Anna), F. Chiodo, M. Borderi (Policlinico Sant' Orsola Malpighi), G. Guaraldi, R. Esposito (Università degli Studi di Modena), C. Ferrari, G. Pasetti (Azienda Ospedaliera di Parma), N. Abrescia, A. Busto, A. Chirianni, M. Gargiulo, C. Izzo, C. Sreglia (Azienda Ospedaliera D. Cotugno), F. Alberici, D. Sacchini (Azienda Unità Sanitaria Locale di Piacenza Ospedale Civile), G. Magnani, G. Zoboli (Arcispedale Santa Maria Nuova).

The following persons and institutions participated in the conduct of this trial: P. Kaul, T. Powell, L. Simmermacher, J. Robinson (University of Cincinnati), L. Alexis, J. Brown, Y. Butler, C. St. Paul (Howard University), L. Meixner, T. Gilbert (University of California, San Diego), J. Kaufman, A. Chall, S. Pedersen, J. Horton (Carolinas Medical Center), T. Lane (Moses Cone Hospital), J. Castro, L. Thompson, L. Colon (University of Miami), B. Gripshover, M. Chance, J. Baum (Case Western Reserve University), D. Wininger, D. Gochnour (Ohio State University), C. Funk, D. Johnson (University of Southern California), I. Matozzo, I. Frank, K. Maffei, D. Kim (University of Pennsylvania), S. Marrero, O. Mendez, I. Torres, N. Rabell (University of Puerto Rico), G. Casey, C. Derkowski (University of Texas, Galveston), C. Fietzer, R. Nelson, K. Fox, R. Sanders (University of Minnesota), W. Wallace (University of Iowa), S. Swindells (University of Nebraska), H. Rominger, J. Richardson (Indiana University Hospital), P. Tebas, D. DeMarco, M. Royal (Washington University), B. Berzins (Northwestern University), H. Kessler (Rush-Presbyterian-St. Luke's Medical Center), J. Forcht, D. Tolenaar, C. Talabucon, C. Gonzalez (New York University/Bellevue), S. Wright, J. Graham (University of Alabama, Birmingham), C. Basler, S. Canmann (University of Colorado Health Sciences Center), P. Cain, S. Stoudt, J. Norris, S. Valle (Stanford University), S. Tedder, C. Hamilton (Duke University Medical Center), T. Flynn, K. Hartman (Massachusetts General Hospital), H. Fitch (Beth Israel Deaconess Medical Center), T. Cooley (Boston Medical Center and Harvard University), J. Frederick, S. Souza (University of Hawaii), D. Baker, A. Weiss, B. Becker, I. Wiggins (Johns Hopkins University), R. Reichman, M. Shoemaker, R. Hewitt, T. O'Hara (University of Rochester Medical Center), J. Lertora, R. Clark, M. Beilke, J. Dumestre (Tulane University), A. Moe, M. Witt, M. Guerrero, T. Maldonado (University of California, Los Angeles), A. Collier, B. Royer, J. Stekler, J. Conley (University of Washington), M. Dolan, E. Chusid, H. Sacks, I. Lowy (Mt. Sinai Medical Center), M. Jacobson, J. Volinski (San Francisco General Hospital), T. Stroberg, R. Gulick, M. Glesby, V. Hughes (Cornell University), R. Arcieri, M. Pirillo, C. Galluzzo, E. Germinario, R. Amici, M. Marzi, A. Nobile, R. Di Nallo, C. Polizzi (Istituto Superiore di Sanita), O. Coronado, G. Fasulo (Ospedale Maggiore), G. Carosi, F. Castelli (Università degli Studi di Brescia, Spedali Civili di Brescia), M. Di Pietro, F. Vichi (Ospedale Santa Maria Annunziata), G. Sterrantino, S. Ambu (Azienda Ospedaliera Careggi), M. Cargnel, P. Meraviglia, F. Niero, A. Capetti, A. D'Arminio Monforte, S. Sollima, C. Balotta (Ospedale Luigi Sacco), S. Delia, M. Ciardi, G. d'Ettore, G. Forcina (Università degli Studi di Roma La Sapienza, Policlinico Umberto I), M. Soranzo, A. Macor (Ospedale Amadeo Di Savoia), D. Bassetti, A. Di Biagio (Università de Genova), L. Minoli, R. Maserati (Istituto di Recupero e Cura a Carattere Scientifico Policlinico S. Matteo), F. Ghinelli, L. Sighinolfi (Azienda Arcispedale Sant' Anna), A. Riva, G. Scalise (Università degli Studi di Ancona Ospedale Umberto I), D. Santoro, E. Rinaldi (Ospedale Sant' Anna), F. Chiodo, M. Borderi (Policlinico Sant' Orsola Malpighi), G. Guaraldi, R. Esposito (Università degli Studi di Modena), C. Ferrari, G. Pasetti (Azienda Ospedaliera di Parma), N. Abrescia, A. Busto, A. Chirianni, M. Gargiulo, C. Izzo, C. Sreglia (Azienda Ospedaliera D. Cotugno), F. Alberici, D. Sacchini (Azienda Unità Sanitaria Locale di Piacenza Ospedale Civile), G. Magnani, G. Zoboli (Arcispedale Santa Maria Nuova).

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