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## EFAVIRENZ PLUS ZIDOVUDINE AND LAMIVUDINE, EFAVIRENZ PLUS INDINAVIR, AND INDINAVIR PLUS ZIDOVUDINE AND LAMIVUDINE IN THE TREATMENT OF HIV-1 INFECTION IN ADULTS

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### ABSTRACT

**Background** Efavirenz is a nonnucleoside reverse-transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1). We compared two regimens containing efavirenz, one with a protease inhibitor and the other with two nucleoside reverse-transcriptase inhibitors, with a standard three-drug regimen.

**Methods** The study subjects were 450 patients who had not previously been treated with lamivudine or any nonnucleoside reverse-transcriptase inhibitor or protease inhibitor. In this open-label study, patients were randomly assigned to one of three regimens: efavirenz (600 mg daily) plus zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily); the protease inhibitor indinavir (800 mg every eight hours) plus zidovudine and lamivudine; or efavirenz plus indinavir (1000 mg every eight hours).

**Results** Suppression of plasma HIV-1 RNA to undetectable levels was achieved in more patients in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors than in the group given indinavir plus nucleoside reverse-transcriptase inhibitors (70 percent vs. 48 percent,  $P < 0.001$ ). The efficacy of the regimen of efavirenz plus indinavir was similar (53 percent) to that of the regimen of indinavir, zidovudine, and lamivudine. CD4 cell counts increased significantly with all combinations (range of increases, 180 to 201 cells per cubic millimeter). More patients discontinued treatment because of adverse events in the group given indinavir and two nucleoside reverse-transcriptase inhibitors than in the group given efavirenz and two nucleoside reverse-transcriptase inhibitors (43 percent vs. 27 percent,  $P = 0.005$ ).

**Conclusions** As antiretroviral therapy in HIV-1-infected adults, the combination of efavirenz, zidovudine, and lamivudine has greater antiviral activity and is better tolerated than the combination of indinavir, zidovudine, and lamivudine. (N Engl J Med 1999;341:1865-73.)

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THE advent of new antiretroviral agents, most notably protease inhibitors, has generated new hope in the fight against human immunodeficiency virus type 1 (HIV-1).<sup>1</sup> The use of a combination of a protease inhibitor plus two nucleoside reverse-transcriptase inhibitors has decreased HIV-1 replication to very low levels, thereby bolstering the immune system, as measured by elevations in CD4 cell counts as well as by better clinical outcomes.<sup>2-4</sup> Enthusiasm for the efficacy of these three-drug regimens that contain protease inhibitors — termed highly active antiretroviral therapy<sup>5-7</sup> — is tempered somewhat by ongoing concern about the large number of pills that must be taken each day, the frequency of dosing,<sup>8,9</sup> interactions among drugs,<sup>10-12</sup> interactions with food,<sup>13</sup> and adverse events.<sup>14</sup> These issues, as well as recent evidence of long-term effects associated with these regimens, including the dysregulation of the metabolism of glucose<sup>15</sup> and lipids as well as the redistribution of fat<sup>16,17</sup> (the lipodystrophy syndrome<sup>18,19</sup>), have spurred further research into new agents and regimens.

The nonnucleoside reverse-transcriptase inhibitors may be alternatives to protease inhibitors in highly active antiretroviral therapy.<sup>20-22</sup> Concern over toxicity<sup>23</sup> and antiviral potency<sup>24,25</sup> has until now limited the

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use of a nonnucleoside reverse-transcriptase inhibitor in place of a protease inhibitor in three-drug combinations. Studies in which two-drug regimens of nucleoside reverse-transcriptase inhibitors were compared with three-drug regimens of two nucleoside reverse-transcriptase inhibitors plus a nonnucleoside reverse-transcriptase inhibitor showed greater efficacy of the three-drug regimens<sup>26-28</sup>; however, the generalizability of the data is limited, because the patients had low levels of plasma HIV-1 RNA at base line and because the antiviral response to treatment with a nonnucleoside reverse-transcriptase inhibitor plus zidovudine and didanosine was not sustained.<sup>29</sup>

In a randomized, open-label study, we compared two new regimens containing the nonnucleoside reverse-transcriptase inhibitor efavirenz with the combination of the protease inhibitor indinavir, zidovudine, and lamivudine with respect to safety, tolerability, and antiretroviral activity. The patients in the study had not previously been treated with lamivudine or any nonnucleoside reverse-transcriptase inhibitor or protease inhibitor.

## METHODS

### Study Design and Patients

This randomized, open-label, multicenter trial compared the combination of indinavir (Crixivan, Merck), zidovudine (Retrovir, Glaxo Wellcome), and lamivudine (EpiVir, Glaxo Wellcome) with either efavirenz (Sustiva, Dupont Pharmaceuticals) plus zidovudine and lamivudine or efavirenz plus indinavir. The primary outcome measure was the percentage of patients with suppression of plasma HIV-1 RNA to undetectable levels at 48 weeks, as determined by a quantitative reverse-transcriptase-polymerase-chain-reaction assay (Amplicor HIV-1 Monitor, Roche Diagnostic Systems) with a limit of detection of 400 copies per milliliter. Measurements of secondary efficacy outcomes included the change in the CD4 cell count from base line; the percentage of patients with suppression of HIV-1 RNA to undetectable levels according to an ultrasensitive assay (Roche) with a limit of detection of less than 50 copies per milliliter; the development of a new acquired immunodeficiency syndrome (AIDS)-defining illness; and death. To determine the safety of the regimens, we assessed the frequency and severity of new treatment-related adverse events (clinical or laboratory), discontinuation of treatment because of adverse events, and changes from base line in clinical characteristics and laboratory values.

The patients were recruited from 34 sites in the United States, Europe, and Canada. They had to be older than 13 years of age, have laboratory evidence of HIV-1 infection, have a CD4 cell count of more than 50 cells per cubic millimeter, have a plasma HIV-1 RNA level of more than 10,000 copies per milliliter, and have no prior exposure to lamivudine or any nonnucleoside reverse-transcriptase inhibitor or protease inhibitor.

The patients received open-label efavirenz (600 mg daily) plus indinavir (1000 mg every eight hours), efavirenz (600 mg daily) plus zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily), or indinavir (800 mg every eight hours) plus zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily). The higher dose of indinavir compensates for its increased catabolism in the presence of efavirenz. Patients for whom a regimen was ineffective or intolerable were not permitted to switch to another regimen.

### Enrollment and Monitoring

Enrollment began in January 1997. The patients had follow-up visits at two, four, and eight weeks and every four weeks thereaf-

ter, at which they underwent a clinical assessment and routine laboratory monitoring, including CD4 cell count and measurement of plasma HIV-1 RNA levels. The ultrasensitive assay was performed at weeks 16, 24, 36, and 48. The severity of adverse events was determined according to the National Cancer Institute Toxicity Criteria.<sup>30</sup> On this scale, a grade of 0 indicates the absence of adverse effects, a grade of 1 a minimal effect, a grade of 2 a mild effect, a grade of 3 a moderate effect, and a grade of 4 a severe effect.

### Statistical Analysis

Using a chi-square test, we compared the rates of response among the treatment groups in terms of the percentage of patients with suppression of plasma HIV-1 RNA levels to less than 400 copies per milliliter (the primary efficacy outcome) as well as the percentage for whom it was less than 50 copies per milliliter. We made comparisons between the two regimens containing efavirenz and the regimen containing indinavir plus two nucleoside reverse-transcriptase inhibitors. For the analysis according to treatment received, we included only patients for whom outcomes were measured at specified time points. The intention-to-treat analysis involved all patients enrolled in the study, including those assigned to a regimen but never treated; in this analysis patients who discontinued treatment were considered to have had no response. Any value that was missing at any point was imputed as a nonresponse, with the exception of missing values for which the preceding and subsequent measurements indicated treatment success, in which case the data were censored.

To assess the antiretroviral activity in patients with high levels of plasma HIV-1 RNA, we performed a post hoc analysis of response rates for the subgroup of patients with base-line levels of more than 100,000 copies per milliliter. We used analysis of variance to compare changes from base line in the levels of plasma HIV-1 RNA and CD4 cell counts. In the analysis of adverse events, we compared the treatments by pairwise chi-square test. All P values reported are two-sided. P values were not adjusted for the repeated analyses.

## RESULTS

### Characteristics of the Patients

A total of 450 patients were enrolled in the study between January and September 1997. The base-line characteristics of the patients were similar among the three groups (Table 1).

### Follow-up and Discontinuation of Treatment

The median duration of follow-up was 47.9 weeks (335 days). Ten percent of the patients (46 of 450) were lost to follow-up or withdrew consent. The duration of follow-up and the percentage of patients lost to follow-up were similar among all treatment groups.

Nineteen of the patients (4 percent) were randomly assigned to a treatment group but never received the treatment. The proportion of patients who discontinued treatment for any reason was higher in the group receiving indinavir plus two nucleoside reverse-transcriptase inhibitors (43 percent) than in the group receiving efavirenz plus two nucleoside reverse-transcriptase inhibitors (27 percent,  $P=0.005$ ). Forty-nine patients (11 percent) discontinued treatment as a result of adverse events (30 in the group given indinavir plus nucleoside reverse-transcriptase inhibitors, 10 in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors, and 9 in the group

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	ALL PATIENTS (N=450)	EFAVIRENZ, ZIDOVUDINE, AND LAMIVUDINE (N= 154)	INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE (N= 148)	EFAVIRENZ AND INDINAVIR (N=148)
Sex — no. of patients (%)				
Male	386 (86)	136 (88)	128 (86)	122 (82)
Female	64 (14)	18 (12)	20 (14)	26 (18)
Mean (±SD) age — yr	36.3±8.2	36.5±8.4	36.9±8.4	35.5±7.9
Race or ethnic group — no. of patients (%)				
Non-Hispanic white	270 (60)	91 (59)	92 (62)	87 (59)
Black	76 (17)	27 (18)	25 (17)	24 (16)
Hispanic or Latino	85 (19)	31 (20)	25 (17)	29 (20)
Other	19 (4)	5 (3)	6 (4)	8 (5)
Prior NRTI therapy other than lamivudine — no. of patients (%)	67 (15)	27 (18)	18 (12)	22 (15)
HIV-1 risk factor — no. of patients (%)†				
Homosexual	307 (68)	115 (75)	99 (67)	93 (63)
Heterosexual	104 (23)	25 (16)	35 (24)	44 (30)
Intravenous drug abuse	43 (10)	12 (8)	17 (11)	14 (9)
Other	20 (4)	10 (6)	2 (1)	8 (5)
CD4 count — cells/mm <sup>3</sup>				
Mean	345	350	341	344
Range	22–1234	35–1234	33–1070	22–994
Plasma HIV-1 RNA — copies/ml				
Mean	58,884	60,256	61,660	56,234
Range	2239–9,549,926	3090–3,235,937	3548–7,943,282	2239–2,344,229
Plasma HIV-1 RNA — log copies/ml				
Mean	4.77	4.78	4.79	4.75
Range	3.35–6.98	3.49–6.51	3.55–6.98	3.35–6.37

\*NRTI denotes nucleoside reverse-transcriptase inhibitor.

†Some patients reported multiple HIV-1 risk factors.

given efavirenz plus indinavir). The rate of discontinuation as a result of adverse events was significantly higher in the three-drug group that included indinavir than in either of the efavirenz groups ( $P < 0.001$ ).

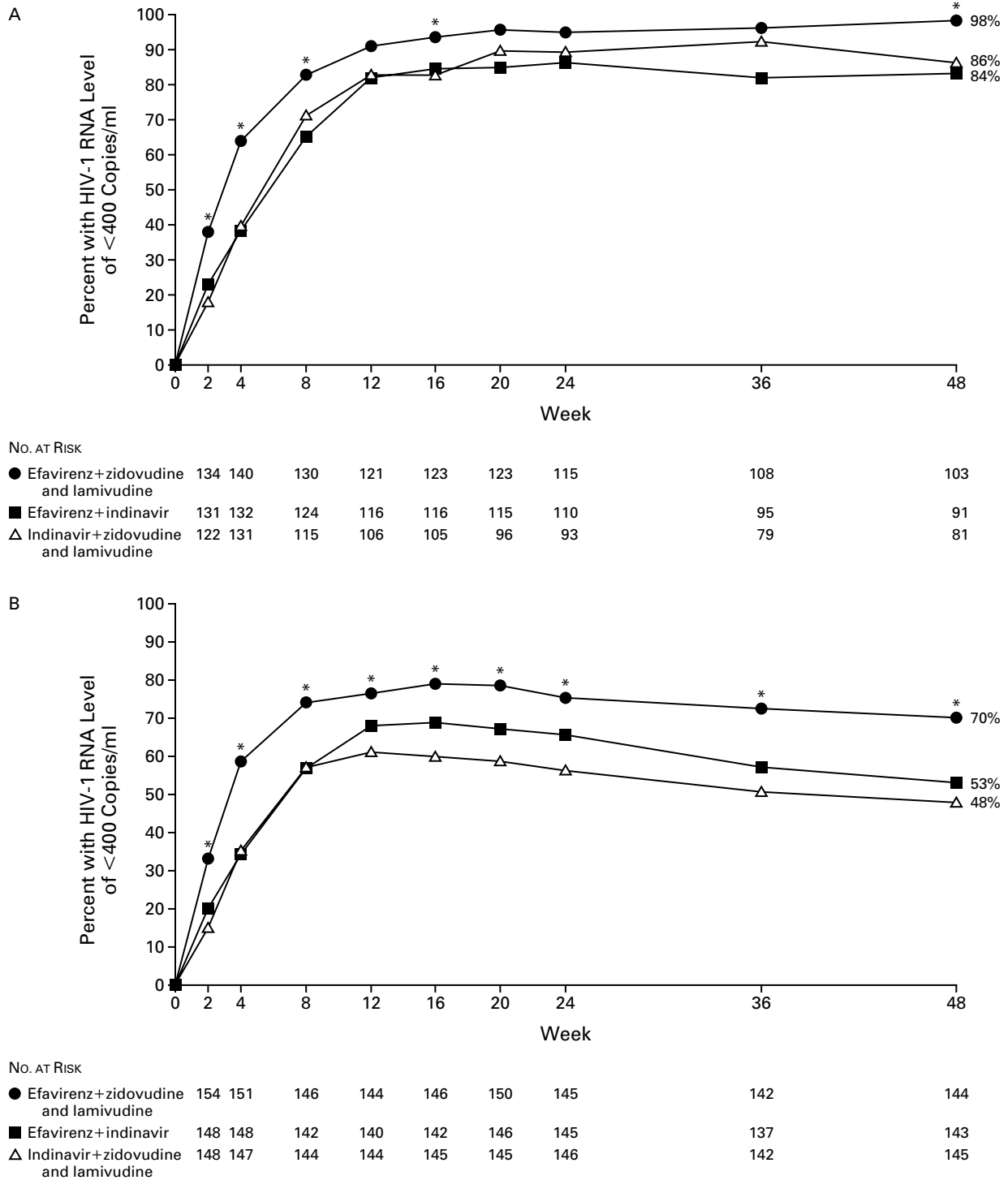
These adverse events were largely gastrointestinal; 9 of the 16 gastrointestinal events were minimal or mild, and 7 were moderate. Most patients who discontinued treatment because of adverse events did so in the first 12 weeks of the study. Ten patients (2 percent) discontinued therapy because of a lack of therapeutic effect or because of a lack of virologic response.

#### Suppression of Plasma HIV-1 RNA to Undetectable Levels

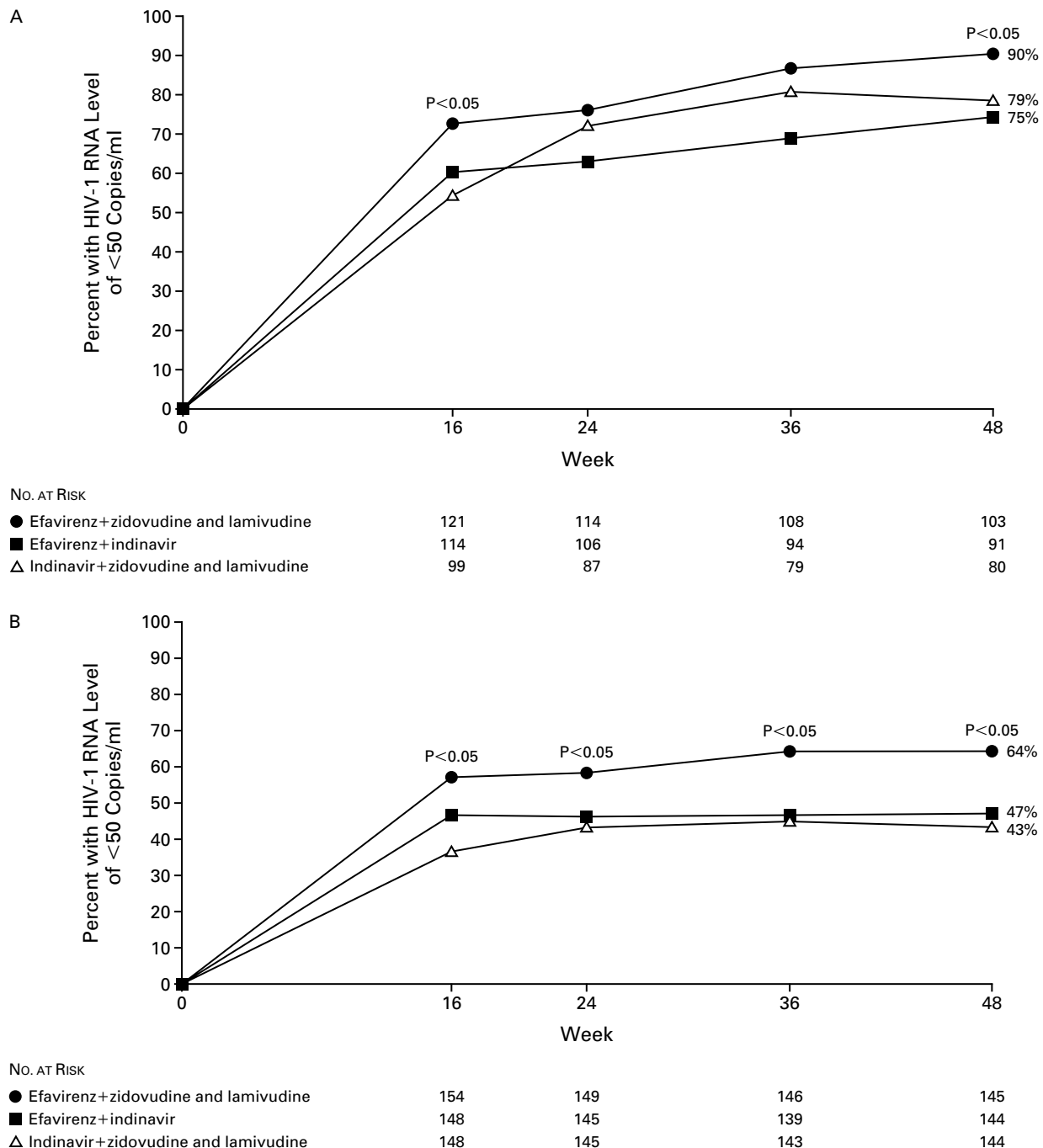
The percentage of patients with suppression of plasma HIV-1 RNA to undetectable levels according to the standard assay (<400 copies per milliliter) is shown in Figure 1. In the analysis according to treatment received, the regimen of efavirenz plus nucleoside reverse-transcriptase inhibitors was more effective than the regimen of indinavir plus nucleoside reverse-transcriptase inhibitors at all points (Fig. 1A). These differences were statistically significant at weeks 2, 4, 8, 16, and 48. The regimen of indinavir plus nucleoside reverse-transcriptase inhibitors was more effective than the regimen of efavirenz plus indinavir at most points, but it was significantly superior only at week 36. In the intention-to-treat analysis, the regi-

men of efavirenz plus nucleoside reverse-transcriptase inhibitors was significantly more effective than the regimen of indinavir plus nucleoside reverse-transcriptase inhibitors at all points (Fig. 1B). Response rates at 48 weeks were 70 percent for the group given efavirenz plus nucleoside reverse-transcriptase inhibitors, 48 percent for the group given indinavir plus nucleoside reverse-transcriptase inhibitors, and 53 percent for the group given efavirenz plus indinavir.

The percentage of patients with plasma HIV-1 RNA levels of less than 50 copies per milliliter according to the ultrasensitive assay is shown in Figure 2. In the analysis according to treatment received, the regimen of efavirenz plus nucleoside reverse-transcriptase inhibitors was more effective than the regimen of indinavir plus nucleoside reverse-transcriptase inhibitors at all points (Fig. 2A), and significantly so at weeks 16 and 48. The response rates were higher in the group given indinavir plus nucleoside reverse-transcriptase inhibitors than in the group given efavirenz plus indinavir at all points after week 16 but were never significantly higher. In the intention-to-treat analysis, the regimen of efavirenz plus nucleoside reverse-transcriptase inhibitors was significantly more effective than the regimen of indinavir plus nucleoside reverse-transcriptase inhibitors at all points (Fig. 2B).



**Figure 1.** Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than 400 Copies per Milliliter, According to an Analysis Based on the Treatment Received (Panel A) and the Intention-to-Treat Analysis (Panel B). Asterisks denote statistically significant differences ( $P < 0.05$ ) from indinavir plus zidovudine and lamivudine.



**Figure 2.** Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than 50 Copies per Milliliter, According to an Analysis Based on the Treatment Received (Panel A) and the Intention-to-Treat Analysis (Panel B).

P values are for the comparison with the group given indinavir plus zidovudine and lamivudine.

**Response Rates Stratified According to Base-Line HIV-1 RNA Levels**

The subgroup analysis of the percentages of patients with HIV-1 RNA levels of less than 50 copies per milliliter at 48 weeks, stratified according to base-line plasma HIV-1 RNA levels, is shown in Figure 3. When we compared regimens in patients with HIV-1 RNA levels of at least 100,000 copies per milliliter at base line, we found that the regimen of efavirenz plus nucleoside reverse-transcriptase inhibitors was significantly more effective than that of indinavir plus nucleoside reverse-transcriptase inhibitors. Response rates in the subgroup of patients with HIV-1 RNA levels of at least 100,000 copies per milliliter at base line were the same as or greater than those in the subgroup of patients with base-line HIV-1 RNA levels of less than 100,000 copies per milliliter for the group given efavirenz plus nucleoside reverse-transcriptase inhibitors.

**Changes from Base Line in CD4 Cell Counts**

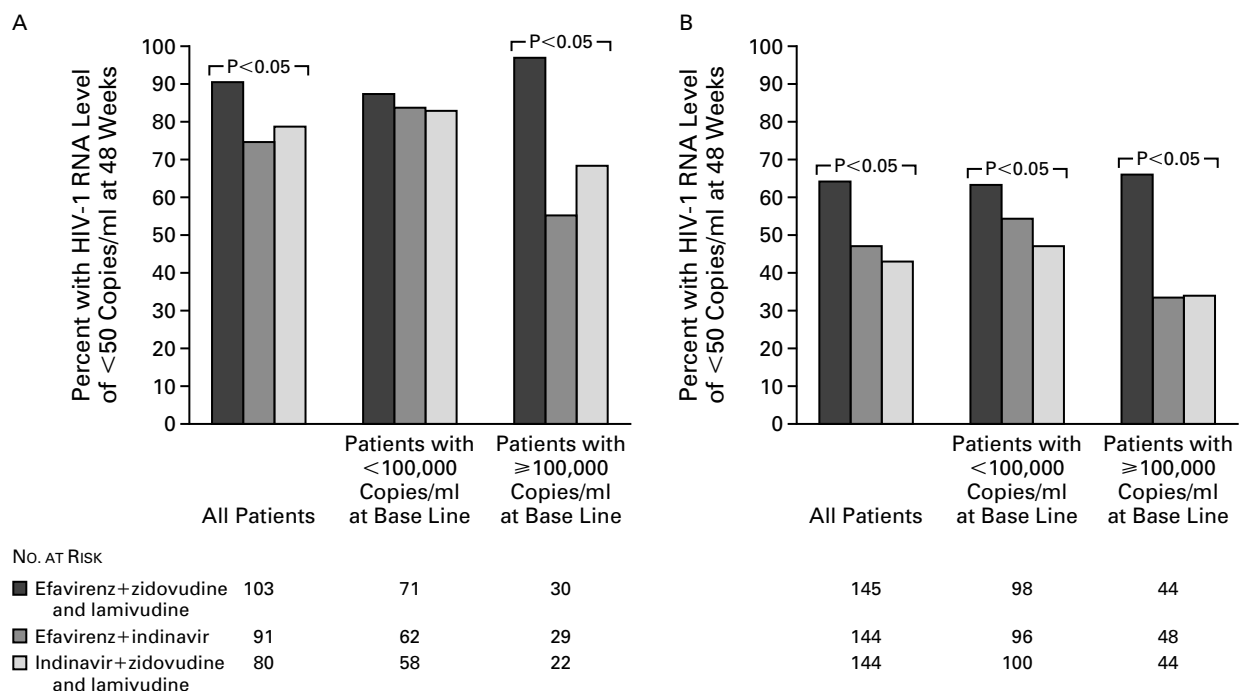
Significant increases from base line in CD4 cell counts were found in all three groups at all points. At 48 weeks of therapy, mean increases of 201, 185, and 180 cells per cubic millimeter were found in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors, the group given indinavir plus nucleoside reverse-transcriptase inhibitors, and the group given efavirenz plus indinavir, respectively (Fig. 4).

**AIDS-Defining Illnesses**

The overall rate of new AIDS-defining events was low; only seven patients in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors, nine patients in the group given indinavir plus nucleoside reverse-transcriptase inhibitors, and three patients in the group given efavirenz plus indinavir had these events. There were no significant differences among the groups.

**Adverse Events**

In patients in all three groups, the most common treatment-related adverse events that were at least mild in severity were nausea, maculopapular rash, vomiting, fatigue, headache, and dizziness. The rates of nausea (27 percent), vomiting (15 percent), pain (predominantly of the flank, 11 percent), and increased bilirubin levels (8 percent) were significantly higher (by no more than 12, 7, and 2 and less than 1 percentage points, respectively) in the group given indinavir plus nucleoside reverse-transcriptase inhibitors than in the two groups treated with the efavirenz-containing regimens. The rates of maculopapular rash and insomnia were higher in the group given efavirenz plus indinavir than in the group given indinavir plus nucleoside reverse-transcriptase inhibitors (16 percent vs. 6 percent and 6 percent vs. 1 percent, respectively). Dizziness and impaired concentration were more



**Figure 3.** Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than 50 Copies per Milliliter at Week 48, Stratified According to Base-Line Plasma HIV-1 RNA Level.

The results were analyzed according to the treatment actually received (Panel A) and according to the intention to treat (Panel B). Base-line samples were not available for three patients who received efavirenz, zidovudine, and lamivudine, one of whom discontinued the study.

frequent in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors than in the group treated with indinavir and nucleoside reverse-transcriptase inhibitors (9 percent vs. 8 percent and 9 percent vs. 8 percent, respectively).

Two distinct groups of adverse events — rash and central nervous system symptoms — were analyzed separately. Both groups receiving the regimens containing efavirenz had higher rates of rash (34 percent for each group) than the group receiving indinavir and two nucleoside reverse-transcriptase inhibitors (18 percent). None of the patients who received efavirenz had a severe rash, and the median duration of rash was 14 days. There were no significant differences among the groups with regard to discontinuation of treatment because of rash. Central nervous system symptoms reported in all treatment groups included, but were not limited to, dizziness, impaired concentration, insomnia, and abnormal dreaming. The incidence was 58 percent in the group given efavirenz plus nucleoside reverse-transcriptase inhibitors, 53 percent in the group given efavirenz plus indinavir, and 26 percent in the group given indinavir plus nucleoside reverse-transcriptase inhibitors ( $P < 0.001$ ). No severe adverse events were reported, and the median duration of symptoms was 19 to 22 days. There were no significant differences among the groups with regard to discontinuation of

treatment as a result of these central nervous system symptoms.

There were no significant differences among treatment groups with regard to clinically notable laboratory abnormalities, except hyperbilirubinemia, which was more frequent in the group given indinavir plus nucleoside reverse-transcriptase inhibitors. One patient in the group given efavirenz plus indinavir died of lymphoma during the first 48 weeks of the study. The death was not considered to be related to the treatment.

DISCUSSION

In this open-label, randomized study, we found that the combination of efavirenz plus zidovudine and lamivudine had better antiretroviral activity and fewer adverse effects than treatment with indinavir plus these same nucleoside reverse-transcriptase inhibitors in HIV-1-infected patients who had base-line CD4 cell counts of more than 50 cells per cubic millimeter and plasma HIV-1 RNA levels of more than 10,000 copies per milliliter. Most patients had not previously received antiretroviral therapy. The two-drug combination of efavirenz plus indinavir had fewer adverse effects than the combination of indinavir and two nucleoside reverse-transcriptase inhibitors, and the efficacy of the two regimens was similar. According to an intention-to-treat analysis, the per-

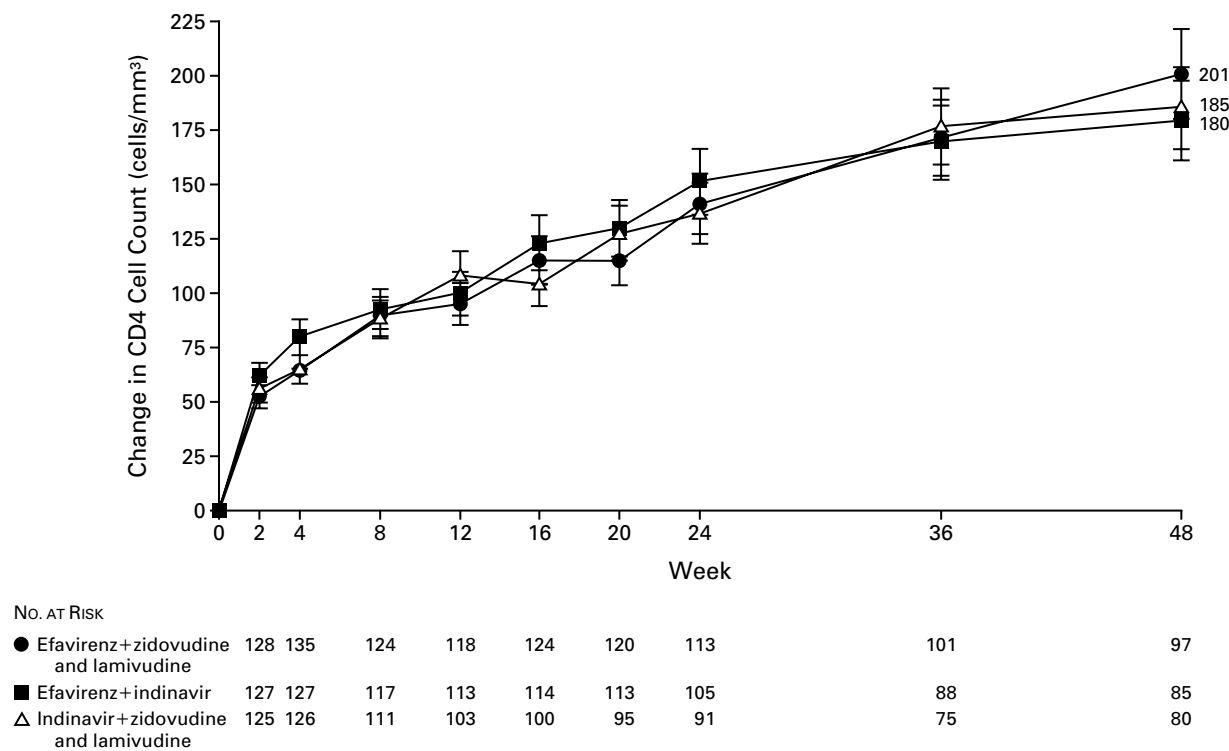


Figure 4. Mean (±SD) Change from Base Line in CD4 Cell Count According to an Analysis Based on the Treatment Received.

centages of patients with plasma HIV-1 RNA levels of less than 400 copies per milliliter at 48 weeks were 70 percent in the group assigned to efavirenz plus nucleoside reverse-transcriptase inhibitors, 53 percent in the group assigned to efavirenz plus indinavir, and 48 percent in the group assigned to indinavir plus nucleoside reverse-transcriptase inhibitors.

The correlation between plasma HIV-1 RNA levels and clinical outcomes is well established, and the use of these levels as a surrogate for efficacy is widely accepted,<sup>31-34</sup> especially when data beyond 24 weeks are available. The clinical significance of these data is reflected in recent modifications to therapeutic guidelines for the treatment of HIV-1 infection. The combination of efavirenz plus two nucleoside reverse-transcriptase inhibitors is now included as a preferred first-line therapy.<sup>35</sup> Corroborating the analysis of the primary efficacy outcome are data obtained through the use of the ultrasensitive plasma HIV-1 RNA assay.<sup>36-38</sup> Maximal antiviral suppression, as demonstrated by decreases in plasma HIV-1 RNA to levels below the limit of quantification of the most sensitive assays, has been shown to be predictive of more sustained antiviral response and is increasingly becoming the goal of antiretroviral therapy.<sup>39</sup> Our subgroup analysis of efficacy outcome, stratified according to base-line levels of plasma HIV-1 RNA, indicated that the combination of efavirenz plus nucleoside reverse-transcriptase inhibitors was just as efficacious in patients with plasma HIV-1 RNA levels of at least 100,000 copies per milliliter at base line.

We performed two separate and complementary analyses of these data. The analysis according to the actual treatment addressed the probability that a patient who continues to receive treatment for any given time will have suppression of viral replication to below quantifiable levels. It did not account for patients who discontinue therapy because of toxicity or a lack of adequate antiviral response.<sup>40</sup> The intention-to-treat analysis (in which a discontinuation of treatment was counted as treatment failure) incorporated such discontinuations and thus is a measure of the effectiveness of the treatment regimens. It did not take into account the reason for discontinuation, however, and thus might overestimate the importance of discontinuations that are not clinically relevant.<sup>41-43</sup> These complementary types of analysis showed the regimen of efavirenz plus zidovudine and lamivudine to be more efficacious than the combination of indinavir and the two nucleoside reverse-transcriptase inhibitors.

There were differences in the rates of discontinuation of treatment. The overall rates of discontinuation were influenced by an unexpectedly high number of patients who dropped out of the study for unknown reasons that were unrelated to safety or efficacy. The higher rate of discontinuation in the group given indinavir plus two nucleoside reverse-transcriptase inhibitors was largely due to gastrointestinal ef-

fects (11 percent). This rate is consistent with data reported for patients receiving for the first time both indinavir and zidovudine concomitantly.<sup>44</sup>

Our study was conducted in an open-label fashion because of the complexity of blinding the patients to the treatment assignments. To do so would have required that all patients ingest a total of 29 pills per day, administered three times a day from five separate bottles. Concern that the complexity of such a dosing schedule would compromise patient compliance and safety prompted the decision to conduct the study in an open-label manner. To balance the open-label nature of the study design, the clinicians and the staff of the central laboratory conducting the efficacy assays were unaware of the treatment assignment, and patients and their physicians were unaware of efficacy results through the first 24 weeks of the study. Although it is impossible to discount with absolute certainty an effect of this design on outcomes, it is highly reassuring that even though patients were aware of their treatment assignments, there were no significant differences among the treatment groups in terms of the number of patients who were lost to follow-up or the number assigned to a treatment group but who never received treatment.

Our findings strongly support the use of efavirenz in HIV-1-infected patients who have not received treatment previously. The superior antiviral activity of the regimen of efavirenz plus two nucleoside reverse-transcriptase inhibitors as compared with a three-drug combination containing a protease inhibitor was not anticipated. Concern that the nonnucleoside reverse-transcriptase inhibitors as a class have less antiviral activity as well as a lower threshold for the development of resistance than protease inhibitors does not appear to be justified for efavirenz. Our results raise the issue of the importance of pharmacologic factors in terms of efficacy. The ratio of the free-drug trough levels of efavirenz in plasma to the amount required in vitro to inhibit 90 percent of protein-free wild-type virus is 26.<sup>45</sup> This fact, coupled with the long terminal half-life of efavirenz (40 to 55 hours), suggests that it is highly unlikely that variability among patients in terms of pharmacokinetics or even an occasional omission of a dose would result in subtherapeutic trough levels and an increased risk of the emergence of a resistant virus. The pharmacokinetic advantages of efavirenz may present a considerable pharmacologic barrier to treatment failure that may be of paramount importance to the success of an antiretroviral regimen.

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## APPENDIX

The following institutions and investigators participated in Study 006: *Center for Special Immunology, Chicago* — D. Berger; *Infectious Diseases, Indianapolis* — J. Black; *Drug Research Services, Metairie, La.* — B. Lutz; *Boulder Community Hospital, Boulder, Colo.* — C. Steinberg; *Palm Beach Research Center, West Palm Beach, Fla.* — B. Miskin; *Center for Special Im-*

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