

## ORIGINAL ARTICLE

# Substitution of Nevirapine, Efavirenz, or Abacavir for Protease Inhibitors in Patients with Human Immunodeficiency Virus Infection

Esteban Martínez, M.D., Juan A. Arnaiz, M.D., Daniel Podzamczar, M.D., David Dalmau, M.D., Esteban Ribera, M.D., Pere Domingo, M.D., Hernando Knobel, M.D., Melcior Riera, M.D., Enric Pedrol, M.D., Lluís Force, M.D., Josep M. Llibre, M.D., Ferran Segura, M.D., Cristóbal Richart, M.D., Cristina Cortés, M.D., Manuel Javaloyas, M.D., Miquel Aranda, M.D., Ana Cruceta, M.D., Elisa de Lazzari, B.Sc., and José M. Gatell, M.D., for the Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team\*

## ABSTRACT

**BACKGROUND**

From the Hospital Clínic, Barcelona (E.M., J.A.A., A.C., E.L., J.M.G.); Hospital de Bellvitge, L'Hospitalet (D.P.); Hospital de Mútua de Terrassa, Terrassa (D.D.); Hospital de Vall d'Hebrón, Barcelona (E.R.); Hospital de la Santa Creu i Sant Pau, Barcelona (P.D.); Hospital del Mar, Barcelona (H.K.); Hospital Son Dureta, Palma de Mallorca (M.R.); Hospital General de Granollers, Granollers (E.P.); Hospital de Mataró, Mataró (L.F.); Hospital Sant Jaume, Calella (J.M.L.); Hospital Parc Taulí, Sabadell (F.S.); Hospital Joan XXIII—Universitat Rovira i Virgili, Tarragona (C.R.); Hospital Creu Roja, L'Hospitalet (C.C.); Hospital de Viladecans, Viladecans (M.J.); and Hospital de Terrassa, Terrassa (M.A.) — all in Spain. Address reprint requests to Dr. Martínez at the Infectious Diseases Unit, Hospital Clínic—Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain, or at esteban@fundsoriano.es.

We assessed the strategy of substituting nevirapine, efavirenz, or abacavir for a protease inhibitor in patients infected with human immunodeficiency virus type 1 (HIV-1) in whom virologic suppression had been achieved.

**METHODS**

We randomly assigned 460 adults who were taking two nucleoside reverse-transcriptase inhibitors and at least one protease inhibitor and whose plasma HIV-1 RNA levels had been less than 200 copies per milliliter for at least the previous six months to switch from the protease inhibitor to nevirapine (155 patients), efavirenz (156), or abacavir (149). The primary end point was death, progression to the acquired immunodeficiency syndrome, or an increase in HIV-1 RNA levels to 200 copies or more per milliliter.

**RESULTS**

At 12 months, the Kaplan–Meier estimates of the likelihood of reaching the end point were 10 percent in the nevirapine group, 6 percent in the efavirenz group, and 13 percent in the abacavir group ( $P=0.10$  according to an intention-to-treat analysis). HIV-1 RNA could be amplified in 21 of the 29 patients in whom virologic failure developed during treatment with study medication (72 percent), and resistance mutations to the study medication and to at least one of the nucleoside reverse-transcriptase inhibitors in the regimen that failed were detected in all but 1 of the 21 patients. Twenty-three of the 29 patients with virologic failure during treatment with study medication had received prior suboptimal therapy with nucleoside reverse-transcriptase inhibitors. Fewer patients in the abacavir group (6 percent) than in the nevirapine group (17 percent) or the efavirenz group (17 percent) discontinued the study medication because of adverse events ( $P=0.01$ ). The proportion of patients with fasting lipid levels warranting therapeutic intervention decreased significantly in the abacavir group, but the prevalence of clinical lipodystrophy did not change significantly in the three groups.

**CONCLUSIONS**

When therapy was switched from a protease inhibitor to nevirapine, efavirenz, or abacavir in patients with virologic suppression, there was a trend toward a higher rate of virologic failure among those given abacavir.

\*Members of the NEFA Study Team are listed in the Appendix.

N Engl J Med 2003;349:1036-46.  
Copyright © 2003 Massachusetts Medical Society.

**T**HE USE OF HIGHLY ACTIVE ANTIRETROVIRAL therapy consisting of two nucleoside reverse-transcriptase inhibitors plus a protease inhibitor led to a sharp decline in the morbidity and mortality associated with human immunodeficiency virus type 1 (HIV-1) infection.<sup>1,2</sup> Therefore, highly active antiretroviral therapy that included a protease inhibitor became the cornerstone of antiretroviral therapy.<sup>3,4</sup> However, protease-inhibitor-based regimens usually involve many pills and food or drink restrictions, may cause drug interactions, and have been associated with morphologic changes and metabolic abnormalities that could increase the risk of cardiovascular disease.<sup>5-9</sup>

In patients who have not previously received antiretroviral therapy, triple antiretroviral regimens containing nevirapine,<sup>10,11</sup> efavirenz,<sup>12,13</sup> or abacavir<sup>14</sup> plus two nucleoside reverse-transcriptase inhibitors have induced virologic responses that are similar to those induced by protease-inhibitor-containing regimens. As compared with protease inhibitors, these agents offer more convenient dosing regimens, involve fewer pills, and result in fewer potentially serious drug interactions. Thus, replacing the protease inhibitor with nevirapine,<sup>15-20</sup> efavirenz,<sup>20-24</sup> or abacavir<sup>25</sup> in an effort to prevent some of the side effects associated with protease-inhibitor therapy and improve the adherence and eventually the long-term efficacy of antiretroviral therapy has become an increasingly popular strategy.<sup>26-28</sup> The relative merits of this approach remain unknown. We compared the efficacy of nevirapine, efavirenz, or abacavir as a substitute for a protease inhibitor in a large group of successfully treated patients with HIV-1 infection.

---

## METHODS

---

### PATIENTS

This multicenter, randomized, open-label clinical trial was carried out at 15 centers in Catalonia and the Balearic Islands in Spain. The protocol was approved by the ethics committee at each center and by the Spanish Medicines Evaluation Agency. Eligible patients were HIV-1-infected adults who were receiving triple antiretroviral therapy consisting of at least one protease inhibitor plus two nucleoside reverse-transcriptase inhibitors, who had had plasma HIV-1 RNA levels below 200 copies per milliliter for at least six months, and who wished to change the protease-inhibitor component of their regimen for some reason. Exclusion criteria were pregnancy

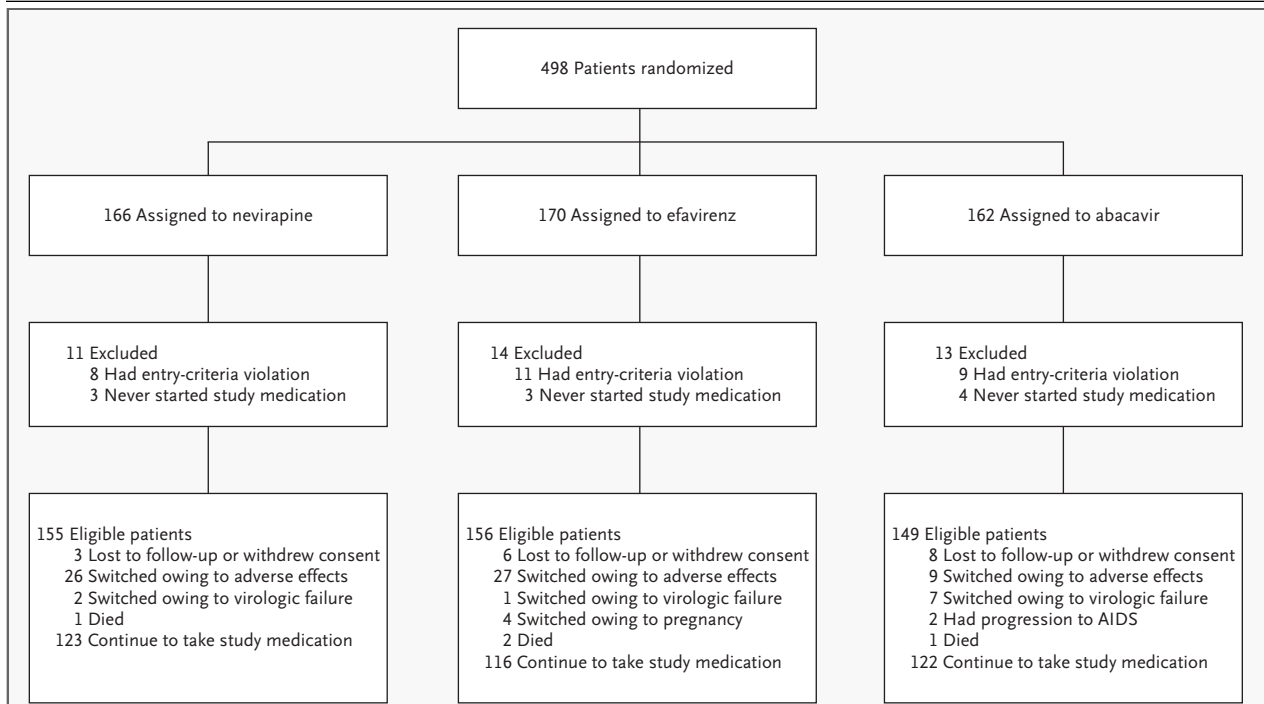
or a wish to become pregnant during the study period, prior treatment with any nonnucleoside reverse-transcriptase inhibitor or abacavir, current treatment with agents known to have potential major interactions with the study drugs, and major psychiatric disease. Written informed consent was obtained from all eligible patients before randomization.

### RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1:1 ratio to receive nevirapine, efavirenz, or abacavir in place of the protease inhibitor used in their current antiretroviral regimen while continuing to take their nucleoside reverse-transcriptase inhibitors. Randomization was centralized. A random sequence was generated by a computer with the use of blocks of variable size that were balanced at each site. Each patient's identification number and treatment group were assigned at the coordinating center after the center had received the randomization form.

After randomization, patients were assessed at base line, 1 month, and 3 months and every 3 months thereafter until they completed at least 12 months of follow-up. At each visit, clinical data were collected and blood specimens were obtained after an overnight fast. Analyses included a complete blood count; CD4 cell count; measurement of plasma HIV-1 RNA, glucose, triglycerides, and total cholesterol; and tests of liver, kidney, and pancreatic function. Plasma levels of high- and low-density lipoprotein cholesterol were measured in a subgroup of patients as part of a metabolic and body-composition study.<sup>29</sup> Routine assays were used at each site throughout the follow-up period.

Safety was assessed through the reporting of adverse clinical events and abnormal laboratory measurements. The severity of toxic effects was assessed with use of the AIDS Clinical Trials Group toxicity grading scale.<sup>30</sup> In patients who discontinued the study medication because of adverse effects, nevirapine and efavirenz were replaced by abacavir and abacavir was replaced by either nevirapine or efavirenz at the discretion of the physician. Clinical assessment and physical examination to detect new body-fat abnormalities or changes in previously recognized ones were also scheduled at each visit, as previously described.<sup>6</sup> The extent of body-fat abnormalities was scored by the physician as moderate or severe if they were clinically evident on examination. For the purpose of analysis, body-fat abnormalities were categorized as lipotrophy or



**Figure 1. Randomization, Eligibility, and Follow-up of the Patients.**

Virologic failure developed in six patients in the nevirapine group and two patients in the efavirenz group after they switched to abacavir because of adverse effects. Virologic failure developed in six additional patients in the nevirapine group, four additional patients in the efavirenz group, and nine additional patients in the abacavir group, but their treatment was not changed.

lipoaccumulation, as previously described.<sup>6</sup> No objective measurements of body composition were performed.

#### DEFINITIONS

Virologic failure was defined by two consecutive measurements of plasma HIV-1 RNA of more than 200 copies per milliliter separated by at least two weeks. In this case therapy could be maintained or changed at the discretion of the physician and the patient could continue in the study at least until he or she completed the 12-month follow-up period. In cases of virologic failure, serum samples were obtained and stored at  $-80^{\circ}\text{C}$  until genotypic resistance tests were performed. All samples were tested with use of the ViroSeq HIV-1 genotyping system according to the manufacturer's instructions (Applied Biosystems). Progression to the acquired immunodeficiency syndrome (AIDS) was defined by the occurrence of any new clinical event included in category C of the 1993 classification of the Centers for Disease Control and Prevention.<sup>31</sup>

#### END POINTS

The primary study end point was death, progression to AIDS, or an HIV-1 RNA level of at least 200 copies per milliliter. According to the protocol, events occurring within 1 month after the 12-month follow-up period were also included in the analysis of end points. Secondary end points were the CD4 cell count, the incidence of side effects, and the occurrence of metabolic and body-fat abnormalities.

#### STATISTICAL ANALYSIS

Patients were followed for the entire trial regardless of whether they prematurely discontinued the assigned therapy. All randomized patients, except those who were found to have violated an entry criterion and those who never started to receive the study medication, were included in the analysis. The inclusion of patients who had entry-criteria violations or who never took the study medication did not significantly affect the overall results. In the intention-to-treat analysis, treatment was considered to have failed in all patients who had progres-

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

Characteristic	Nevirapine (N=155)	Efavirenz (N=156)	Abacavir (N=149)
Age — yr			
Median	39	38	40
Range	23–73	21–69	24–71
Male sex — no. (%)	119 (77)	117 (75)	113 (76)
Route of HIV infection — no. (%)			
Male homosexual sex	43 (28)	46 (29)	37 (25)
Heterosexual sex	42 (27)	49 (31)	45 (30)
Injection-drug use	65 (42)	53 (34)	53 (36)
Other or unknown	5 (3)	8 (5)	14 (9)
Acquired immunodeficiency syndrome — no. (%)	55 (35)	52 (33)	56 (38)
CD4 cells per mm <sup>3</sup>			
Median	508	558	544
Interquartile range	332–755	356–751	366–688
Protease inhibitor withdrawn — no. (%)			
Indinavir	104 (67)	87 (56)	87 (58)
Nelfinavir	39 (25)	54 (35)	42 (28)
Ritonavir	0	4 (3)	11 (7)
Saquinavir	3 (2)	4 (3)	6 (4)
Combinations with low-dose ritonavir	9 (6)	7 (4)	3 (2)
Nucleoside reverse-transcriptase inhibitor continued — no. (%)			
Stavudine + lamivudine	85 (55)	93 (60)	81 (54)
Zidovudine + lamivudine	53 (34)	43 (28)	49 (33)
Stavudine + didanosine	11 (7)	14 (9)	15 (10)
Zidovudine + didanosine	4 (3)	6 (4)	3 (2)
Other	2 (1)	0	1 (1)
Duration of highly active antiretroviral therapy — mo			
Median	29	31	30
Range	6–53	6–69	10–64
Prior suboptimal therapy with nucleoside reverse-transcriptase inhibitors — no. (%)	78 (50)	90 (58)	69 (46)
Fasting metabolic values — no. (%)			
Glucose >126 mg/dl (7 mmol/liter)	5 (3)	13 (8)	6 (4)
Total cholesterol >240 mg/dl (6.2 mmol/liter)	33 (21)	37 (24)	37 (25)
Triglycerides >400 mg/dl (4.5 mmol/liter)	20 (13)	14 (9)	11 (7)
Moderate or severe lipodystrophy — no. (%)			
Lipoaccumulation	31 (20)	28 (18)	31 (21)
Lipoatrophy	40 (26)	42 (27)	43 (29)

\* There were no significant differences among the groups.

sion to AIDS, died, or had detectable HIV-1 RNA levels (i.e., levels of at least 200 copies per milliliter), but not in patients who discontinued the study medication as long as HIV-1 RNA levels remained below 200 copies per milliliter; data on patients who withdrew consent or who were lost to follow-up were censored. In the analysis of patients according to the treatment received, treatment failure was defined by progression to AIDS, death, or detectable viral levels during treatment; data on patients who withdrew consent, were lost to follow-up, or switched or stopped study medication were

censored. Switches in nucleoside reverse-transcriptase inhibitors were not considered to indicate treatment failure as long as HIV-1 RNA levels remained below 200 copies per milliliter.

The sample size was calculated on the basis of virologic end points, because very few clinical events and deaths were expected in this population. The sample size was computed to detect equivalence among the treatment groups in the proportion of patients with plasma viral RNA levels below 200 copies per milliliter at the end of the study. For this purpose, we assumed that the proportion of pa-

**Table 2. Outcome of Therapy.**

Outcome	Nevirapine (N=155)	Efavirenz (N=156)	Abacavir (N=149)
	<i>no. of patients</i>		
Death	1	2	1
Progression to AIDS*	0	0	2
Virologic failure	14	7	16
While taking study medication	8	5	16
After switching study medication	6	2	0
Lost to follow-up	3	6	8
Switched study medication without virologic failure	20	29	9
Response; still taking study medication at 12 mo†	117	112	113

\* AIDS denotes acquired immunodeficiency syndrome.

† Six additional patients in the nevirapine group, four in the efavirenz group, and nine in the abacavir group continued to take study medication at 12 months despite the development of virologic failure.

tients with virologic suppression during treatment would remain similar to the proportion with suppression of HIV-1 while protease-inhibitor-based antiretroviral therapy was continued.<sup>32,33</sup> Equivalence was considered to be proved if the upper limit of the 95 percent confidence interval of the difference among the proportions of patients with fewer than 200 copies of HIV-1 RNA per milliliter in each group was 13.5 percent or less (that is, 15 percent of the expected rate of success of protease-inhibitor regimens of 90 percent).<sup>34,35</sup> A total of 148 patients per group was required for the equivalence assessment with a two-sided alpha level of 0.05 and a statistical power of 90 percent.

Statistical analysis was performed with the use of Stata software (release 7.0). Chi-square or Fisher's exact tests were used to compare the proportions of patients who dropped out and demographic characteristics among the treatment groups. Differences in continuous variables among the groups were analyzed with use of the Kruskal-Wallis test, and Wilcoxon's signed-rank test was used for comparisons with base-line values. The time to virologic failure was estimated with use of the Kaplan-Meier product-limit method. The equality of the distributions of the times to an event among the groups was estimated with use of the generalized log-rank test. Cox proportional-hazards models were used to describe the univariate factors associated with reaching a study end point. Simple comparisons were made with use of a two-sided alpha

level of 0.05; each of the three pairwise comparisons used a two-sided significance level of 0.0167.

## RESULTS

### POPULATION

Between December 1999 and February 2001, 498 patients underwent randomization and 460 were found eligible for the study (Fig. 1). The base-line characteristics of the patients were not significantly different among the groups (Table 1). The median CD4 cell count was 544 per cubic millimeter (interquartile range, 366 to 688). Thirty-five percent of the patients had previously had category C events. Approximately half the patients in each group had received antiretroviral therapy that included one or two nucleoside reverse-transcriptase inhibitors before they received protease-inhibitor-containing therapy. Three patients in the nevirapine group, six in the efavirenz group, and eight in the abacavir group were lost to follow-up or withdrew consent ( $P=0.27$  by the chi-square test) (Fig. 1).

### OUTCOMES

The outcomes of therapy are shown in Table 2. At 12 months, the Kaplan-Meier estimates of the percentage of patients who had reached a protocol-defined end point were 10 percent in the nevirapine group, 6 percent in the efavirenz group, and 13 percent in the abacavir group according to an intention-to-treat analysis ( $P=0.10$  by a generalized log-rank test), and 7 percent, 5 percent, and 14 percent, respectively, in an analysis conducted according to the treatment received ( $P=0.03$  by a generalized log-rank test) (Fig. 2). In an exploratory subanalysis, we found that patients who had received prior suboptimal antiretroviral therapies (single or double therapies with nucleoside reverse-transcriptase inhibitors) were overrepresented among the patients who had virologic failure while they were taking the study medication: 5 of 8 such patients in the nevirapine group (62 percent), 4 of 5 in the efavirenz group (80 percent), and 14 of 16 in the abacavir group (88 percent) (global  $P=0.002$  by the log-rank test; hazard ratio, 3.76 for patients with prior single or double therapy with nucleoside reverse-transcriptase inhibitors; 95 percent confidence interval, 1.53 to 9.23;  $P=0.004$ ).

There were no significant differences among the groups in the median CD4 cell counts ( $P>0.40$  at each time point by the Kruskal-Wallis test) (see Supplementary Appendix 1, available with the full

text of this article at <http://www.nejm.org>). At 12 months, the median increases from base line were 50, 49, and 39 CD4 cells per cubic millimeter in the nevirapine, efavirenz, and abacavir groups, respectively ( $P=0.48$  by the Kruskal–Wallis test).

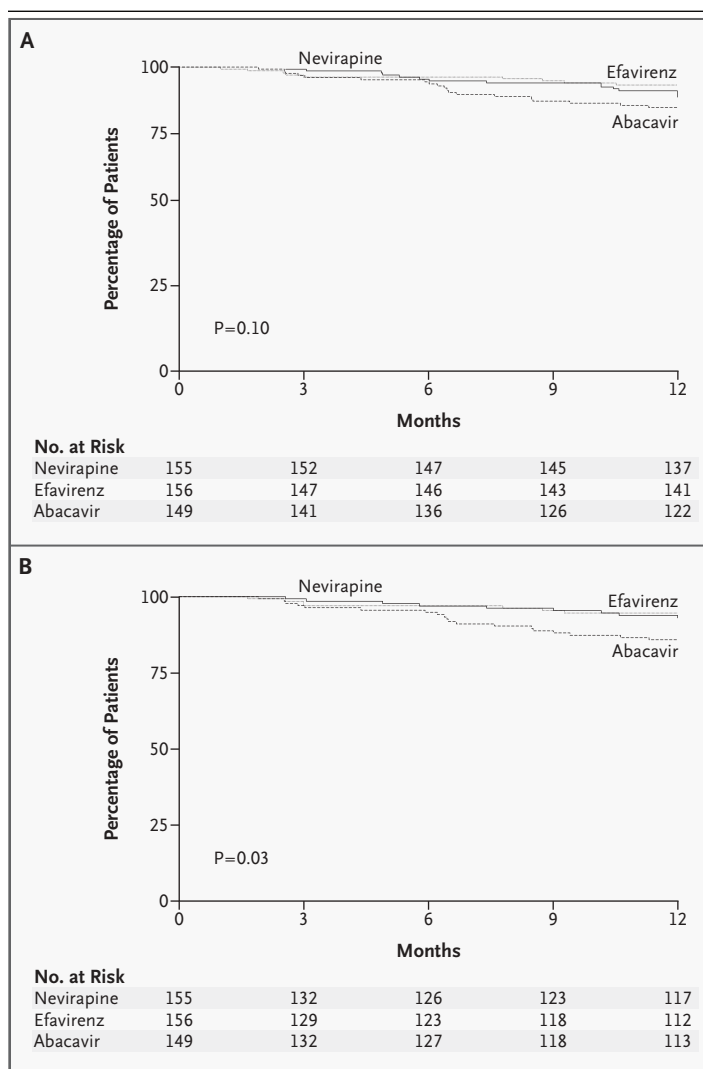
During the study, two patients (both assigned to receive abacavir) had progression to AIDS (as defined by the occurrence of histoplasmosis in one and tuberculosis in the other) and four patients died (one each in the nevirapine and abacavir groups and two in the efavirenz group). Causes of death were a traffic accident (in the nevirapine group), sudden death and end-stage liver disease (in the efavirenz group), and colonic neoplasia (in the abacavir group).

HIV-1 RNA could be amplified in 21 of the 29 patients in whom virologic failure developed during treatment with study medication (72 percent): 5 of 8 in the nevirapine group, 2 of 5 in the efavirenz group, and 14 of 16 in the abacavir group. In the remaining eight patients, the viral load was less

than 1000 RNA copies per milliliter and HIV-1 RNA could not be amplified. All 5 patients in the nevirapine group, both patients in the efavirenz group, and all 14 patients in the abacavir group with amplifiable HIV-1 RNA had mutations associated with resistance to the study drugs (K103N, V106A, and Y181C alone or in combination in the nevirapine and efavirenz groups and M41L, K65R, D67N, T69N, K70R, L74V, M184V, L210W, T215Y, and K219Q alone or in combination in the abacavir group). Moreover, all 5 patients in the nevirapine group, all 2 in the efavirenz group, and all 14 in the abacavir group had resistance mutations to at least one of the nucleoside reverse-transcriptase inhibitors included in the regimen that failed (M41L, K65R, D67N, T69N, K70R, M184V, L210W, T215Y, and K219Q).

**Figure 2.** Kaplan–Meier Estimates of the Likelihood of Reaching the End Point of Death, Progression to the Acquired Immunodeficiency Syndrome, or an RNA Level above 200 Copies per Milliliter, According to an Intention-to-Treat Analysis (Panel A) and an Analysis According to the Treatment Received (Panel B).

In Panel A, the intention-to-treat analysis revealed the following: a global  $P=0.10$  by the log-rank test;  $P=0.10$  for the comparison of abacavir with efavirenz,  $P=0.68$  for the comparison of abacavir with nevirapine, and  $P=0.55$  for the comparison of efavirenz with nevirapine (for each pairwise comparison, a two-sided  $P$  value of 0.0167 was considered to indicate statistical significance). Cox proportional-hazards regression analysis showed a hazard ratio of 1.00 for abacavir (the reference group), a hazard ratio of 0.43 for the comparison of efavirenz with abacavir (95 percent confidence interval, 0.20 to 0.96), and a hazard ratio of 0.71 for the comparison of nevirapine with abacavir (95 percent confidence interval, 0.36 to 1.40) (overall  $P=0.11$ ). In Panel B, the analysis according to the treatment received revealed the following: a global  $P=0.03$  by the log-rank test;  $P=0.06$  for the comparison of abacavir with efavirenz,  $P=0.15$  for the comparison of abacavir with nevirapine, and  $P=0.97$  for the comparison of efavirenz with nevirapine (for each pairwise comparison, a two-sided  $P$  value of 0.0167 was considered to indicate statistical significance). Cox proportional-hazards regression analysis showed a hazard ratio of 1.00 for abacavir (the reference group), a hazard ratio of 0.38 for the comparison of efavirenz with abacavir (95 percent confidence interval, 0.16 to 0.90), and a hazard ratio of 0.46 for the comparison of nevirapine with abacavir (95 percent confidence interval, 0.21 to 1.03) (overall  $P=0.04$ ).



**TOLERABILITY**

The overall incidence of adverse events was significantly lower (61 patients, or 41 percent) in the abacavir group than in the nevirapine group (83 patients, or 54 percent) or the efavirenz group (89 patients, or 57 percent) ( $P=0.03$  by the chi-square test) (Table 3). The incidence of adverse effects was not influenced by the use of specific combinations of nucleoside reverse-transcriptase inhibitors. Significantly fewer patients in the abacavir group (9 patients, or 6 percent) than in the nevirapine group (26 patients, or 17 percent) or the efavirenz group (27 patients, or 17 percent) ( $P=0.01$  by the chi-square test) (Table 3) discontinued the study medication because of adverse events.

The median fasting plasma triglyceride values at each time point were not significantly different among the groups (Fig. 3A). However, the proportion of patients with plasma triglyceride levels above 400 mg per deciliter (4.5 mmol per liter) was significantly smaller at 12 months in the abacavir group (4 patients, or 4 percent) than in the nevirapine group (13 patients, or 12 percent) or the efavirenz group (13 patients, or 13 percent) ( $P=0.05$  by Fisher's exact test) (see Supplementary Appendix 2, available with the full text of this article at <http://www.nejm.org>).

The median fasting plasma cholesterol values

were significantly lower in the abacavir group than in the other two groups at all follow-up visits ( $P<0.001$  by the Kruskal–Wallis test) (Fig. 3B). The proportion of patients with plasma cholesterol levels above 240 mg per deciliter (6.2 mmol per liter) was also significantly lower in the abacavir group than in the other two groups ( $P<0.001$  at 3 months,  $P=0.09$  at 6 months,  $P=0.005$  at 9 months, and  $P<0.001$  at 12 months by Fisher's exact test) (see Supplementary Appendix 2). The median fasting plasma glucose levels were significantly higher in the efavirenz group than in the nevirapine or abacavir group at all follow-up visits ( $P\leq 0.01$  by the Kruskal–Wallis test). The proportion of patients with plasma glucose levels above 126 mg per deciliter (7 mmol per liter) at the end of the study was 3 percent in the nevirapine group and 9 percent in each of the other two groups ( $P=0.09$  by Fisher's exact test).

Overall, the proportion of patients with moderate or severe lipoaccumulation changed from 20 percent at base line to 16 percent at 12 months ( $P>0.50$  by the chi-square test) (see Supplementary Appendix 3, available with the full text of this article at <http://www.nejm.org>). In contrast, the proportion of patients with moderate or severe lipodystrophy changed from 27 percent at base line to 33 percent at 12 months ( $P>0.50$  by the chi-square

**Table 3. Number of Patients Who Had One or More Adverse Events.\***

Adverse Event	Nevirapine (N=155)			Efavirenz (N=156)			Abacavir (N=149)		
	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation
<i>number of patients (percent)</i>									
Clinical									
Neuropsychiatric	11	6	6	48	22	19	14	1	0
Cutaneous	20	13	12	11	3	3	7	0	0
Gastrointestinal	6	2	0	8	4	4	12	2	1
Systemic†	7	1	1	5	2	0	10	8	8
Other	25	8	1	11	5	1	12	3	0
Laboratory									
Increased aminotransferase levels	12	6	4	4	1	0	5	1	0
Hyperglycemia	2	2	2	2	2	0	1	1	0
<b>Total</b>	<b>83 (54)‡</b>	<b>38</b>	<b>26 (17)§</b>	<b>89 (57)‡</b>	<b>39</b>	<b>27 (17)§</b>	<b>61 (41)‡</b>	<b>16</b>	<b>9 (6)§</b>

\* A grade 3 event was defined as severe, and a grade 4 event as life-threatening.

† Systemic adverse events included hypersensitivity reactions.

‡  $P=0.03$  by the chi-square test.

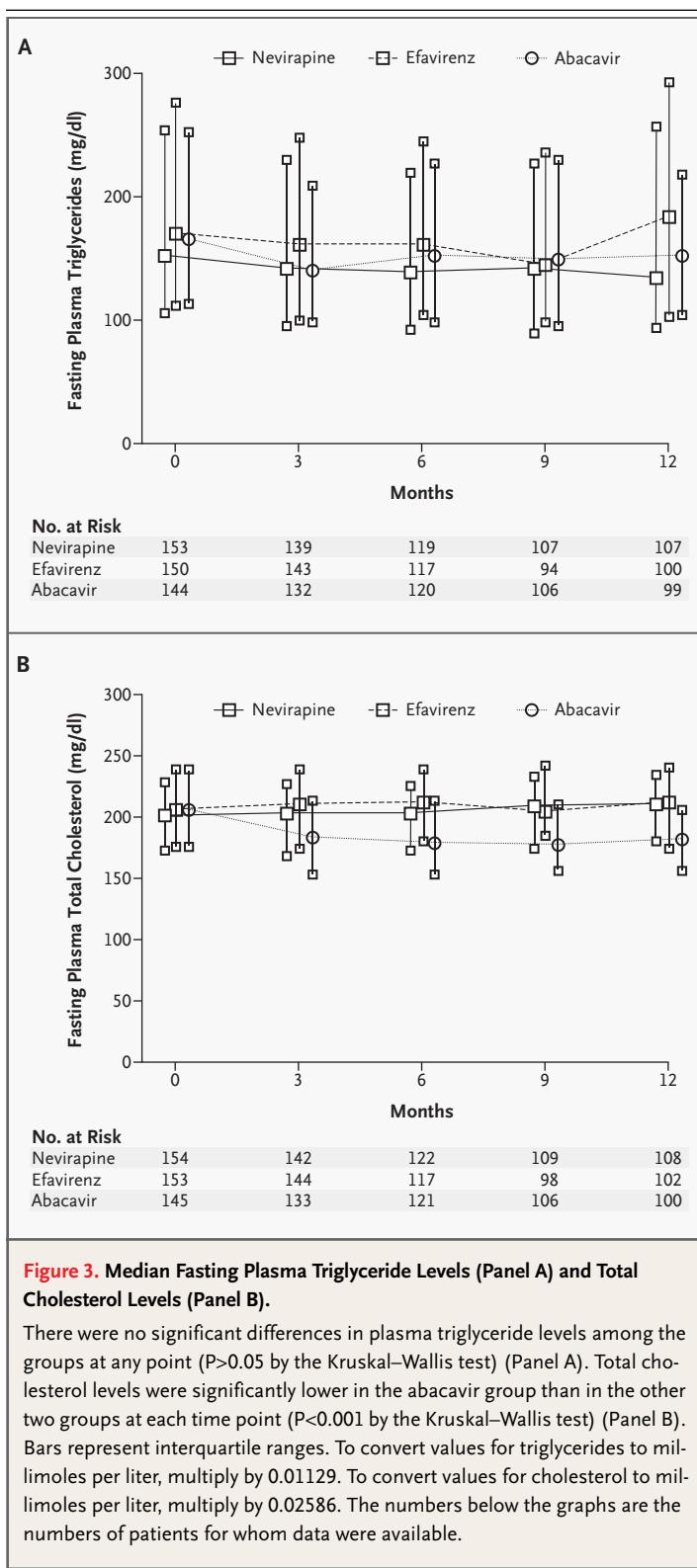
§  $P=0.01$  by the chi-square test.

test) (see Supplementary Appendix 3). There were no significant differences among the groups in the proportions of patients with moderate or severe lip accumulation or lipatrophy during the study.

## DISCUSSION

There was a trend toward a higher failure rate when abacavir rather than nevirapine or efavirenz replaced the protease-inhibitor component of a regimen that included two nucleoside reverse-transcriptase inhibitors and had resulted in sustained virologic suppression. In the intention-to-treat analysis, discontinuation of study medication was not counted as a treatment failure as long as HIV-1 RNA levels remained below 200 copies per milliliter. The implications of virologic failure, with its potential for the emergence of persistent resistance, differ substantially from those of treatment failure, because the side effects of drugs are usually reversible and an alternative drug can be substituted while the viral load remains undetectable.

The response rates did not differ significantly between the nevirapine and efavirenz groups. Consequently, our data do not confirm previous cohort studies showing virologic superiority of efavirenz over nevirapine,<sup>36,37</sup> at least among patients with a response. Moreover, the noninferiority of nevirapine as compared with efavirenz has been demonstrated in a recent randomized trial in patients who had not previously received antiretroviral therapy.<sup>38</sup> In our study, virologic failures occurred almost exclusively among patients with prior suboptimal therapy with nucleoside reverse-transcriptase inhibitors. When genotypic analysis of resistance could be performed, resistance mutations to the study drugs and to nucleoside reverse-transcriptase inhibitors could be detected in almost all such patients. Cross-resistance between abacavir and other nucleoside reverse-transcriptase inhibitors may explain in part the higher rate of virologic failure in the abacavir group and among the patients assigned to nevirapine or efavirenz who switched to abacavir because of adverse effects. A similar trend toward a higher rate of virologic failure has already been described among patients who switched from protease inhibitors to abacavir, as compared with patients who continued to receive protease inhibitors as part of highly active antiretroviral therapy.<sup>39</sup> A history of suboptimal antiretroviral therapy has also been associated



with a higher risk of virologic failure among patients who switch from protease inhibitors to non-nucleoside reverse-transcriptase inhibitors.<sup>40,41</sup> Altogether, these data suggest that preexisting resistance mutations may facilitate the emergence of virus that is resistant to the replacement drug. Thus, changing from a protease-inhibitor-containing regimen to a simpler regimen will have the highest likelihood of maintaining viral suppression when used in patients with no history of suboptimal therapy or virologic failure, particularly when the replacement drug is abacavir.

Simplifying antiretroviral therapy in patients in stable condition by switching from a protease inhibitor to nevirapine, efavirenz, or abacavir carries a risk of adverse effects that are due to the replacement drugs. Approximately half our patients had adverse effects related to the study drugs, although such effects led to the discontinuation of the drug in only a minority of them. The rate of discontinuation due to adverse effects was similar in the nevirapine and efavirenz groups and was significantly higher than the rate in the abacavir group. The types of adverse effects in each group were among those commonly expected.

In contrast to previous smaller studies<sup>15-25</sup> in which patients switched drugs predominantly to reverse metabolic or body-fat abnormalities, the primary reason for the switch in our study was to simplify the regimen. Because only a moderate proportion of patients had metabolic or body-fat abnormalities at base line, any conclusions about the effect of each study drug on these abnormalities should be drawn with caution. In addition, measurements of high- and low-density lipoprotein cholesterol levels were made only in the patients in the metabolic and body-composition substudy.<sup>29</sup> Although the patients in the substudy were not exactly representative of the whole population, a significantly lower proportion of patients with plasma cholesterol and triglyceride levels warranting therapeutic intervention was found in the abacavir group than in the nevirapine or efavirenz group. The proportion of patients with moderate or severe lipoac-

cumulation tended to decrease during the 12-month study, whereas that of patients with moderate or severe lipoatrophy tended to increase in all three groups, although there were no significant differences among the groups at any time. Although clinically evident lipoatrophy and lipoaccumulation decreased in some patients during the study, new cases also appeared in each group. These data are in accordance with similar, smaller studies that included objective measurements of body composition.<sup>19,20</sup> Therefore, our data do not support switching from a protease inhibitor to nevirapine, efavirenz, or abacavir as a useful strategy to ameliorate body-fat abnormalities.

In summary, simplification of the highly active antiretroviral therapy regimen in patients with a sustained virologic response had a higher probability of maintaining viral suppression if nevirapine or efavirenz was substituted for a protease inhibitor than if abacavir was substituted, particularly in patients with a prior suboptimal response to therapy with nucleoside reverse-transcriptase inhibitors. However, the rates of viral suppression among patients who had not had prior suboptimal therapy with nucleoside reverse-transcriptase inhibitors were similar for the three drugs. Approximately 50 percent of the patients in each group had adverse effects related to the study drug. Abacavir had a lower incidence of adverse effects that led to the discontinuation of the study drug and caused a greater decrease in plasma lipid levels than did nevirapine or efavirenz.

Supported in part by grants from the Comisión Interministerial de Ciencia y Tecnología (SAF 1998-0021 and SAF 2001-2591), the Grupo Consolidado from the Generalitat de Catalunya (2001-0777), and the Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo (PI02590 and Red Temática Cooperativa de Investigación en SIDA RIS G03/173); and by unrestricted research grants from Boehringer Ingelheim, Bristol-Myers Squibb, and GlaxoSmithKline (Spain).

Dr. Domingo reports having received lecture fees from Bristol-Myers Squibb and GlaxoSmithKline; Dr. Gatell lecture fees or grant support from Bristol-Myers Squibb, Boehringer Ingelheim, Dupont, GlaxoSmithKline, and Merck; Dr. Martínez grant support from Bristol-Myers Squibb, Boehringer Ingelheim, Dupont, and GlaxoSmithKline; and Dr. Arnaiz grant support from Bristol-Myers Squibb, Boehringer Ingelheim, and GlaxoSmithKline.

#### APPENDIX

The members of NEFA Study Team were as follows: **Trial chairs** — E. Martínez, J.M. Gatell; **Trial Coordinators and Monitors** — J.A. Arnaiz, A. Cruceta, J. Pich, S. Varea; **Trial Statistician** — E. de Lazzari; **Data Safety and Monitoring Board** — X. Carné, J.M. Miró, J.J. Aponte; **Participating Centers and Investigators** (all in Spain) — Hospital de Bellvitge, L'Hospitalet — D. Podzamczar, B. Rosón; Hospital Clínic, Barcelona — E. Martínez, A. Milinkovic, J.B. Pérez-Cuevas, J.L. Blanco, M. Arnedo, A. León, M. Laguno, J. Mallolas, T. Pumarola, J.M. Gatell; Hospital Creu Roja, L'Hospitalet — C. Cortés, I. García; Hospital General de Granollers, Granollers — E. Pedrol, C. Font; Hospital Joan XXIII-Universitat Rovira i Virgili, Tarragona — C. Richart, J. Peraire, C. Viladés, F. Vidal; Hospital del Mar, Barcelona — H. Knobel, A. González; Hospital de Mataró, Mataró — L. Force, P. Barrufet; Hospital de Mútua de Terrassa, Terrassa — D. Dalmau, A. Ochoa de Echagüen, M. Xercavins; Hospital Parc Taulí, Sabadell — F. Segura, E. Antón; Hospital Sant Jaume, Calella — J.M. Llibre; Hospital de la Santa Creu i Sant Pau, Barcelona — P. Domingo, M. Barceló, F. Montero; Hospital Son Dureta, Palma de Mallorca — M. Riera, M. Leyes; Hospital de Terrassa, Terrassa — M. Aranda; Hospital Vall d'Hebron, Barcelona — E. Ribera, M. Crespo; Hospital de Viladecans, Viladecans — M. Javaloyas.

## REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
2. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998;352:1725-30.
3. Rubio R, Berenguer J, Miro JM, et al. Recomendaciones de GESIDA/Plan Nacional sobre el Sida respecto al tratamiento antiretroviral en pacientes adultos infectados por el virus de la inmunodeficiencia humana en el año 2002. *Enferm Infecc Microbiol Clin* 2002;20:244-303.
4. Yeni PG, Hammer SM, Carpenter C, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2002;288:222-35.
5. Flexner C. HIV-protease inhibitors. *N Engl J Med* 1998;338:1281-92.
6. Martinez E, Mocroft A, Garcia-Viejo MA, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001;357:592-8.
7. Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000;32:111-23.
8. Pujol RM, Domingo P, Matias-Guiu X, et al. HIV-1 protease inhibitor-associated partial lipodystrophy: clinicopathologic review of 14 cases. *J Am Acad Dermatol* 2000;42:193-8.
9. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360:1747-8.
10. Van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003;17:987-99.
11. Podzamczak D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients: the COMBINE study. *Antivir Ther* 2002;7:81-90.
12. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999;341:1865-73.
13. Squires KE, Thiry A, Giordano M, et al. Atazanavir (ATV) QD and Efavirenz (EFV) QD with fixed-dose ZDV+3TC: comparison of antiviral efficacy and safety through week 24 (A1424-034). In: Program and abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., September 27-30, 2002. Washington, D.C.: American Society for Microbiology, 2002:11-1076. abstract.
14. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: a randomized equivalence trial. *JAMA* 2001;9:1155-63.
15. Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS* 1999;13:805-10.
16. Dieleman JP, Gyssens IC, Sturkenboom MJCM, Niesters HGM, van der Ende ME. Substituting nevirapine for protease inhibitors because of intolerance. *AIDS* 1999;13:1423-4.
17. Barreiro P, Soriano V, Blanco F, et al. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. *AIDS* 2000;14:807-12.
18. Raffi F, Bonnet B, Ferré V, et al. Substitution of a nonnucleoside reverse transcriptase inhibitor for a protease inhibitor in the treatment of patients with undetectable plasma human immunodeficiency virus type 1 RNA. *Clin Infect Dis* 2000;31:1274-8.
19. Ruiz L, Negro E, Domingo P, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J Acquir Immune Defic Syndr* 2001;27:229-36.
20. Negro E, Cruz L, Paredes R, et al. Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus and long-lasting viral suppression. *Clin Infect Dis* 2002;34:504-10.
21. Martinez E, Garcia-Viejo MA, Blanco JL, et al. Impact of switching from human immunodeficiency virus type 1 protease inhibitors to efavirenz in successfully treated adults with lipodystrophy. *Clin Infect Dis* 2000;31:1266-73.
22. Rey D, Schmitt MP, Partisani M, et al. Efavirenz as a substitute for protease inhibitors in HIV-1-infected patients with undetectable plasma viral load on HAART: a median follow-up of 64 weeks. *J Acquir Immune Defic Syndr* 2001;27:459-62.
23. Knechten H, Stürner KH, Höhn C, Braun P. Switch to efavirenz in a protease inhibitor-containing regimen. *HIV Clin Trials* 2001;2:200-4.
24. Hirschel B, Flepp M, Bucher HC, et al. Switching from protease inhibitors to efavirenz: differences in efficacy and tolerance among risk groups: a case-control study from the Swiss HIV Cohort. *AIDS* 2002;16:381-5.
25. Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based highly active antiretroviral therapy in HIV-1-infected patients with undetectable plasma HIV-1 RNA. *AIDS* 2001;15:1517-26.
26. Henry K. The case for more cautious, patient-focused antiretroviral therapy. *Ann Intern Med* 2000;132:306-11.
27. Murphy RL, Smith WJ. Switch studies: a review. *HIV Med* 2002;3:146-55.
28. Drechsler H, Powderly WG. Switching effective antiretroviral therapy: a review. *Clin Infect Dis* 2002;35:1219-30.
29. Fisac C, Fumero E, Crespo M, et al. Metabolic and body composition changes in patients switching from a protease inhibitor-containing regimen to abacavir, efavirenz or nevirapine: 12-month results of a randomized study (LIPNEFA). In: Program and abstracts of the 14th International AIDS Conference, Barcelona, Spain, July 7-12, 2002: B7. abstract.
30. AIDS Clinical Trials Group. Table for grading severity of adult adverse experiences. August 1992. (Accessed June 30, 2003, at <http://aactg.s-3.com/members/adulttox.htm>.)
31. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;41(RR-17):1-19.
32. Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV-infected subjects with undetectable plasma HIV RNA after triple-drug therapy. *N Engl J Med* 1998;339:1261-8.
33. Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. *N Engl J Med* 1998;339:1269-76.
34. Casagrande JT, Pike MC. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics* 1978;34:483-6.
35. Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. *Cancer Treat Rep* 1978;62:1037-40.
36. Phillips AN, Pradier C, Lazzarin A, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. *AIDS* 2001;15:2385-95.
37. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. *AIDS* 2002;16:53-61.
38. van Leth F, Hassink E, Phanuphak P, et al. Results of the 2NN Study: a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs

- combined, with stavudine and lamivudine. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003: 176. abstract.
- 39.** Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. *J Infect Dis* 2002;185:1251-60.
- 40.** Masquelier B, Neau D, Chêne G, et al. Mechanism of virologic failure after substitution of a protease inhibitor by nevirapine in patients with suppressed plasma HIV-1 RNA. *J Acquir Immune Defic Syndr* 2001; 28:309-12.
- 41.** Dieleman JP, Sturkenboom MCJM, Wit FW, et al. Low risk of treatment failure after substitution of nevirapine for protease inhibitors among human immunodeficiency virus-infected patients with virus suppression. *J Infect Dis* 2002;185:1261-8.

*Copyright © 2003 Massachusetts Medical Society.*