

## ORIGINAL ARTICLE

# Peginterferon Alfa-2a plus Ribavirin for Chronic Hepatitis C Virus Infection in HIV-Infected Patients

Francesca J. Torriani, M.D., Maribel Rodriguez-Torres, M.D.,  
Jürgen K. Rockstroh, M.D., Eduardo Lissen, M.D., Juan Gonzalez-García, M.D.,  
Adriano Lazzarin, M.D., Giampiero Carosi, M.D., Joseph Sasadeusz, M.D.,  
Christine Katlama, M.D., Julio Montaner, M.D., Hoel Sette, Jr., M.D.,  
Sharon Passe, M.S., Jean De Pampphilis, Ph.D., Frank Duff, M.D.,  
Uschi Marion Schrenk, M.D., and Douglas T. Dieterich, M.D.,  
for the APRICOT Study Group\*

## ABSTRACT

**BACKGROUND**

From the Department of Medicine, Division of Infectious Diseases, University of California, San Diego (F.J.T.); the Fundacion de Investigacion de Diego, Santurce, Puerto Rico (M.R.-T.); the University of Bonn, Bonn, Germany (J.K.R.); Virgen del Rocío University Hospital, Seville, Spain (E.L.); Unidad Virus de la Inmunodeficiencia Humana, Hospital Universitario La Paz, Madrid (J.G.-G.); Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Vita-Salute University, Milan (A.L.); the Department of Infectious and Tropical Diseases, University of Brescia, Brescia, Italy (G.C.); Alfred Hospital, Melbourne, Victoria, Australia (J.S.); Groupe Hospitalier de la Pitié-Salpêtrière, Paris (C.K.); the University of British Columbia, Vancouver, Canada (J.M.); Instituto de Infectologia Emilio Ribas, São Paulo (H.S.); Roche, Nutley, N.J. (S.P., J.D.P., F.D.); Roche, Basel, Switzerland (U.M.S.); and Mount Sinai School of Medicine, New York (D.T.D.). Address reprint requests to Dr. Torriani at the University of California, San Diego, AntiViral Research Center, 150 W. Washington St., Suite 100, San Diego, CA 92103, or at ftorriani@ucsd.edu.

Hepatitis C virus (HCV) infection is highly prevalent and is associated with substantial morbidity and mortality among persons infected with the human immunodeficiency virus (HIV). We compared the efficacy and safety of pegylated interferon alfa-2a (peginterferon alfa-2a) plus either ribavirin or placebo with those of interferon alfa-2a plus ribavirin for the treatment of chronic HCV infection in patients who were also infected with HIV.

**METHODS**

A total of 868 persons who were infected with both HIV and HCV and who had not previously been treated with interferon or ribavirin were randomly assigned to receive one of three regimens: peginterferon alfa-2a (180 µg per week) plus ribavirin (800 mg per day), peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU three times a week) plus ribavirin. Patients were treated for 48 weeks and followed for an additional 24 weeks. The primary end point was a sustained virologic response (defined as a serum HCV RNA level below 50 IU per milliliter at the end of follow-up, at week 72).

**RESULTS**

The overall rate of sustained virologic response was significantly higher among the recipients of peginterferon alfa-2a plus ribavirin than among those assigned to interferon alfa-2a plus ribavirin (40 percent vs. 12 percent,  $P < 0.001$ ), or peginterferon alfa-2a plus placebo (40 percent vs. 20 percent,  $P < 0.001$ ). Among patients infected with HCV genotype 1, the rates of sustained virologic response were 29 percent with peginterferon alfa-2a plus ribavirin, 14 percent with peginterferon alfa-2a plus placebo, and 7 percent with interferon alfa-2a plus ribavirin. The corresponding rates among patients infected with HCV genotype 2 or 3 were 62 percent, 36 percent, and 20 percent. Neutropenia and thrombocytopenia were more common among patients treated with regimens that contained peginterferon alfa-2a, and anemia was more common among patients treated with regimens containing ribavirin.

**CONCLUSIONS**

Among patients infected with both HIV and HCV, the combination of peginterferon alfa-2a plus ribavirin was significantly more effective than either interferon alfa-2a plus ribavirin or peginterferon alfa-2a monotherapy.

\*Other members of the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) study group are listed in the Appendix.

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**P**OTENT ANTIRETROVIRAL THERAPY HAS reduced the morbidity and mortality associated with untreated human immunodeficiency virus (HIV) infection.<sup>1,2</sup> At the same time, the pattern of morbidity and mortality among HIV-infected persons has shifted, and clinicians responsible for the care of HIV-infected persons have been confronted with new challenges. Complications associated with concurrent hepatitis C virus (HCV) infection have emerged as one of the most frequent and complex issues in the care of patients with HIV infection and the acquired immunodeficiency syndrome (AIDS).<sup>3,4</sup>

The current standard of care for chronic infection with HCV in persons without other infections is pegylated interferon (peginterferon) plus ribavirin.<sup>5</sup> This combination eradicates HCV infection and produces sustained virologic responses in 54 to 63 percent of patients.<sup>6-8</sup> The efficacy of this combination of drugs in persons with both HIV and HCV infection has not been established. In the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), we studied the efficacy and safety of combination therapy with peginterferon alfa-2a plus ribavirin in people coinfecting with HCV and HIV in an international, randomized, placebo-controlled trial.

## METHODS

### SELECTION OF PATIENTS

To be eligible for the study, patients had to be more than 18 years of age, to be infected with both HIV and HCV, and to have anti-HCV antibodies in serum, detectable serum levels of HCV RNA (>600 IU per milliliter), elevated serum alanine aminotransferase levels documented on two or more occasions within the previous 12 months, findings on liver biopsy within the past 15 months that were consistent with the presence of chronic hepatitis C infection, and compensated liver disease (without compromise of liver function or clinically important portal hypertension).

The presence of HIV type 1 (HIV-1) disease was confirmed by detection of anti-HIV-1 antibodies or HIV-1 RNA in serum (Amplicor HIV-1 Monitor Test, version 1.5). Patients with CD4+ cell counts of 200 per cubic millimeter or higher were eligible regardless of the HIV RNA level; those with CD4+ cell counts between 100 per cubic millimeter and 199 per cubic millimeter were eligible if their HIV-1 RNA load was less than 5000 copies per milliliter.

Subjects were required either to have been receiving stable antiretroviral therapy for at least six weeks before study entry, with no changes expected for the first eight weeks of the study, or not to have received any antiretroviral therapy for at least eight weeks before randomization and to be able to delay the initiation of antiretroviral therapy for at least six weeks. For the remainder of the study, changes to an existing antiretroviral therapy regimen or initiation of antiretroviral therapy was permitted at the discretion of the investigator.

Subjects with the following conditions were excluded: an active HIV-related opportunistic infection or cancer; an absolute neutrophil count below 1500 per cubic millimeter; a platelet count below 70,000 per cubic millimeter; a hemoglobin level below 11 g per deciliter for women, or below 12 g per deciliter for men; a serum creatinine level more than 1.5 times the upper limit of normal; concurrent infection with hepatitis A or B virus; evidence of decompensated liver disease; severe psychiatric disease, especially depression; clinically significant coexisting medical conditions; and, for women, pregnancy or unwillingness to practice contraception. Participants were also excluded if they had previously received interferon or ribavirin.

### STUDY DESIGN

The study was conducted at 95 centers in 19 countries between June 2000 and September 2003. Patients were randomly assigned in a 1:1:1 ratio to 48 weeks of treatment with one of three regimens: subcutaneous interferon alfa-2a (Roferon-A, Roche), at a dose of 3 million IU given three times per week, plus oral ribavirin (Copegus, Roche), at a dose of 400 mg given twice daily (total daily dose, 800 mg); peginterferon alfa-2a (Pegasys, Roche), at a dose of 180 µg given once weekly, plus oral placebo twice daily; or peginterferon alfa-2a plus oral ribavirin. The 48-week treatment period was followed by a 24-week observation period. The sponsor, investigators, and subjects were blinded to the assignment to ribavirin or placebo in the peginterferon alfa-2a groups. Treatment assignment was centralized and performed with the Pocock-Simon covariate adaptive procedure.<sup>9</sup> Stratification factors included the HCV genotype (genotype 1 vs. other genotypes), the CD4+ cell count (<200 per cubic millimeter vs. ≥200 per cubic millimeter), HIV treatment (antiretroviral therapy vs. no antiretroviral therapy), histologic findings on liver biopsy (cirrhosis vs. no cirrhosis), qualifying alanine ami-

notransferase quotient (the patient's value at baseline divided by the upper limit of normal for the assay), and geographic region. Baseline findings on liver biopsy were scored by local pathologists using the Ishak Modified Histological Activity Scoring System.<sup>10</sup> With this system, biopsy findings are assigned scores for necroinflammatory grade (0 to 18, with 0 indicating no necroinflammation) and fibrosis stage (0 indicates no fibrosis and 6 probable or definite cirrhosis). The sum of the necroinflammatory and fibrosis scores is referred to as the total histologic-activity index score.

Institutional review boards at participating centers approved the protocol. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices guidelines. The study was designed by the sponsor in collaboration with consultant physicians with expertise in the treatment of HCV and HIV infections and in clinical-trial design. Data were collected by the APRICOT study group and analyzed by the sponsor and the authors. Decisions regarding all aspects of the manuscript were made by the authors, and no limitations on publication were imposed by the sponsor.

#### ASSESSMENT OF EFFICACY AND END POINTS

Serum HCV RNA was measured by means of a qualitative polymerase-chain-reaction (PCR) assay (Cobas Amplicor HCV Test, version 2.0, Roche Diagnostics; limit of detection, 50 IU per milliliter) at weeks 4, 12, 24, 36, and 48 during treatment and after 12 and 24 weeks of follow-up after the cessation of study treatment (study weeks 60 and 72). HCV RNA was quantified by PCR (Cobas Amplicor HCV Monitor Test, version 2.0; limit of detection, 600 IU per milliliter) in all patients with detectable HCV RNA. The primary efficacy end point was a sustained virologic response, defined as a serum HCV RNA level below the limit of detection of the assay (<50 IU per milliliter) at the end of 24 weeks of follow-up. In patients without an HCV RNA measurement at week 72, treatment was considered to have failed. An early virologic response was defined as an undetectable serum HCV RNA level on quantitative PCR assay or a decrease of more than 2 log<sub>10</sub> in the serum HCV RNA level on quantitative PCR assay at week 12 or 24. HCV and HIV RNA determinations and HCV genotyping (Versant HCV Genotype Assay, Bayer) were performed by Cenetron Diagnostics, Cedar Creek, Texas.

#### ASSESSMENT OF SAFETY

Safety was assessed by means of physical examinations, laboratory tests, and spontaneous reports of clinical adverse events during patients' visits to the clinic at weeks 1, 2, 4, 6, 8, and 12, at six-week intervals thereafter during treatment, and at weeks 52, 60, and 72 during follow-up.

Stepwise reductions in the dose of peginterferon alfa-2a to 135, 90, or 45 µg per week, stepwise reductions in the dose of interferon alfa-2a to 2.25 or 1.5 million units three times per week, and sequential reductions in the dose of ribavirin or ribavirin placebo by 200 mg per day, but to no lower than 600 mg per day, were allowed when necessary to manage clinically significant adverse events or laboratory abnormalities, according to a defined protocol. If the adverse effect or abnormality improved or resolved, a return to the initial dose was permitted at the discretion of the investigator. Patients could continue to receive peginterferon alfa-2a or interferon alfa-2a if ribavirin was discontinued. The use of granulocyte colony-stimulating factors and erythropoietin was permitted to manage hematologic adverse events.

#### STATISTICAL ANALYSIS

The study treatment was discontinued if peginterferon alfa-2a or interferon alfa-2a was permanently stopped. The analysis was conducted according to the intention-to-treat principle. Patients who missed the study visit at week 72 were considered to have had treatment failure. The population for the efficacy analysis included all patients who underwent randomization and received at least one dose of either study drug. The safety analysis included all treated patients who had at least one safety evaluation after baseline. Patients who withdrew from treatment were encouraged to return for follow-up appointments.

For comparisons between two treatment groups, the study had 80 percent power to detect an improvement in the rate of sustained virologic response from 30 percent to 45 percent, with a two-sided significance level of 0.025. As defined in the protocol, a closed testing procedure allowed for three pairwise comparisons between the treatment groups.<sup>11</sup> The global hypothesis of no differences among treatment groups was to be tested first at a significance level of 0.05. If it was rejected, each of the three pairwise comparisons was to be tested at a significance level of 0.05. The Cochran-Mantel-

Haenszel test was used, with stratification according to geographic region, HCV genotype, and CD4+ cell count; multiple logistic-regression analysis was used to examine the effect of all five stratification factors on sustained virologic response and to confirm the results of the Cochran–Mantel–Haenszel test.

Stepwise and backward logistic-regression analyses were used to identify pretreatment factors that were predictive of a sustained virologic response. All P values are two-sided.

## RESULTS

### DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

Of 1158 subjects screened, 868 were randomly assigned to a treatment group, and 860 received study medication. The distribution of participants in the trial is shown in Figure 1. The characteristics of the treatment groups were similar at baseline (Table 1). The patients were predominantly white and male and had well-controlled HIV infection. Sixteen percent had cirrhosis or bridging fibrosis.

### VIROLOGIC RESPONSE

The overall rate of sustained virologic response at the end of follow-up, the primary efficacy end point, was significantly higher among patients treated with peginterferon alfa-2a plus ribavirin than among those treated with interferon alfa-2a plus ribavirin (40 percent vs. 12 percent; odds ratio, 5.40; 97.5 percent confidence interval, 3.20 to 9.12;  $P < 0.001$ ) or peginterferon alfa-2a plus placebo (40 percent vs. 20 percent; odds ratio, 2.89; 97.5 percent confidence interval, 1.83 to 4.58;  $P < 0.001$ ) (Fig. 2B). The rate of sustained virologic response was significantly lower among recipients of interferon alfa-2a plus ribavirin than among recipients of peginterferon alfa-2a plus placebo (odds ratio, 0.53; 97.5 percent confidence interval, 0.30 to 0.91;  $P = 0.008$ ).

When the patients were grouped according to HCV genotype, the rates of sustained virologic response reflected those in the overall study population, with the highest rates consistently observed among recipients of peginterferon alfa-2a plus ribavirin (Fig. 2B). Patients infected with HCV genotype 1 had consistently lower rates of sustained virologic response than those infected with HCV genotype 2 or 3. Both overall and among patients infected with HCV genotype 1, patients in all three

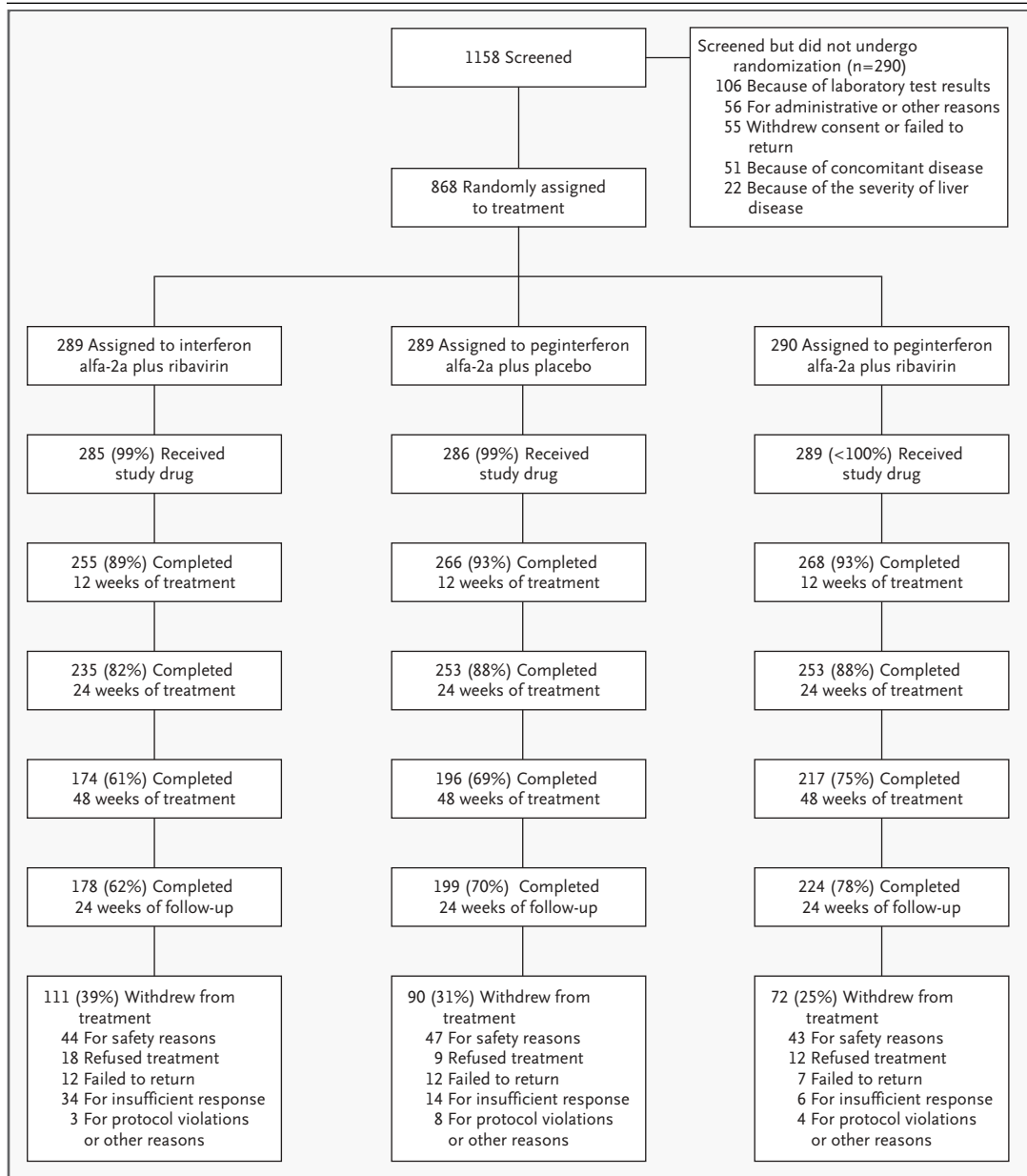
treatment groups who had high pretreatment HCV RNA levels ( $>800,000$  IU per milliliter) had consistently lower rates of sustained virologic response than did those with lower pretreatment HCV RNA levels (Fig. 2C). The pretreatment HCV RNA level did not affect the rate of sustained virologic response among patients infected with genotype 2 or 3.

### Independent Factors Associated with a Sustained Virologic Response

A prospectively defined multiple logistic-regression analysis was used to identify pretreatment factors that were predictive of a sustained virologic response among patients treated with peginterferon alfa-2a plus ribavirin. The factors analyzed were age, sex, race (white vs. nonwhite), body-surface area, HCV RNA level, total histologic-activity index score, qualifying alanine aminotransferase quotient (the alanine aminotransferase value divided by upper limit of normal), HCV genotype (1 vs. others), CD4+ cell count, use or nonuse of antiretroviral therapy, and histologic findings on liver biopsy (presence or absence of cirrhosis). The final model included two factors that are associated with independently and significantly increased odds of a sustained virologic response: an HCV genotype other than 1 (odds ratio, 3.37; 95 percent confidence interval, 1.96 to 5.80;  $P < 0.001$ ) and a baseline HCV RNA level of 800,000 IU or less per milliliter (odds ratio, 3.56; 95 percent confidence interval, 2.00 to 6.36;  $P < 0.001$ ). HIV-related factors including the CD4+ cell count and the use or nonuse of antiretroviral therapy, which are variables of particular interest in this population, did not meet the criteria for inclusion in the final model.

### Predictive Value of an Early Virologic Response

Patients with an early virologic response, defined as an undetectable HCV RNA level or a decrease of 2 log or more in the HCV RNA level by week 12, were more likely to achieve a sustained virologic response (Fig. 3). Of patients who had an early virologic response by week 12, 30 percent in the group given interferon alfa-2a plus ribavirin, 37 percent of those assigned to peginterferon alfa-2a plus placebo, and 56 percent of those given peginterferon alfa-2a plus ribavirin had sustained virologic responses at week 72. Only two patients without an early virologic response went on to have a sustained virologic response; one was a patient with HCV genotype 1b who became HCV RNA-negative at



**Figure 1. Study Enrollment and Outcomes.**

Of the eight patients who underwent randomization but were not treated, seven declined treatment and one failed to return to the study center. One patient who was randomly assigned to peginterferon alfa-2a plus ribavirin was mistakenly treated with interferon alfa-2a plus ribavirin (classified in the group given interferon alfa-2a plus ribavirin). Patients who withdrew from treatment were encouraged to return at weeks 48, 60, and 72 for follow-up assessments.

week 24, and the other was a patient infected with HCV genotype 4 who became HCV RNA-negative at week 36. Overall, only 2 percent or less of the patients in each treatment group who did not have an early response went on to have a sustained response. When an early virologic response was de-

finied as one occurring by week 24, the results were similar.

*Safety*

The frequency of dose reductions in response to clinical adverse events was generally similar among

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

| Characteristic  | Interferon Alfa-2a plus Ribavirin (N=285) | Peginterferon Alfa-2a plus Placebo (N=286) | Peginterferon Alfa-2a plus Ribavirin (N=289) |
|---|---|--|--|
| Sex — no. (%)   |   |  |  |
| Male  | 231 (81)                                  | 234 (82)                                   | 232 (80)                                     |
| Female  | 54 (19)                                   | 52 (18)                                    | 57 (20)                                      |
| Age — yr  | 40.1±7.6                                  | 40.0±7.4                                   | 39.7±7.9                                     |
| Weight — kg   | 74.6±13.2                                 | 73.2±13.6                                  | 72.1±13.7                                    |
| Body-mass index†  | 24.9±4.2                                  | 24.7±3.8                                   | 24.2±4.1                                     |
| Race — no. (%)  |   |  |  |
| White   | 223 (78)                                  | 225 (79)                                   | 231 (80)                                     |
| Black   | 30 (11)                                   | 28 (10)                                    | 31 (11)                                      |
| Asian   | 0   | 3 (1)                                      | 4 (1)  |
| Other   | 32 (11)                                   | 30 (10)                                    | 23 (8)                                       |
| Mode of infection — no. (%)                             |   |  |  |
| Injection-drug use                                      | 201 (71)                                  | 178 (62)                                   | 180 (62)                                     |
| Sexual exposure   | 44 (15)                                   | 54 (19)                                    | 56 (19)                                      |
| Transfusion   | 13 (5)                                    | 22 (8)                                     | 24 (8)                                       |
| Unknown or other  | 27 (9)                                    | 32 (11)                                    | 29 (10)                                      |
| Qualifying alanine aminotransferase quotient — no. (%)‡ |   |  |  |
| ≤1.0  | 0   | 1 (<1)                                     | 1 (<1)                                       |
| >1.0–1.5  | 46 (16)                                   | 53 (19)                                    | 56 (19)                                      |
| >1.5–3.0  | 137 (48)                                  | 134 (47)                                   | 126 (44)                                     |
| >3.0–7.0  | 92 (32)                                   | 90 (31)                                    | 95 (33)                                      |
| >7.0  | 10 (4)                                    | 8 (3)                                      | 11 (4)                                       |
| Serum HCV RNA   |   |  |  |
| Mean — IU/ml  | 5,200,000±6,000,000                       | 6,400,000±6,400,000                        | 5,600,000±6,400,000                          |
| >800,000 IU/ml — no. (%)                                | 203 (71)                                  | 206 (72)                                   | 208 (72)                                     |
| HCV genotype — no. (%)                                  |   |  |  |
| 1   | 171 (60)                                  | 175 (61)                                   | 176 (61)                                     |
| 2   | 14 (5)                                    | 17 (6)                                     | 13 (4)                                       |
| 3   | 75 (26)                                   | 73 (26)                                    | 82 (28)                                      |
| 4   | 24 (8)                                    | 20 (7)                                     | 16 (6)                                       |
| Other   | 1 (<1)                                    | 1 (<1)                                     | 2 (1)  |
| Total histologic-activity index score§                  | 8.0±3.8                                   | 7.9±3.7                                    | 8.0±3.8                                      |
| Total cirrhosis or bridging fibrosis — no. (%)          | 45 (16)                                   | 45 (16)                                    | 44 (15)                                      |
| Fibrosis stage 4 — no. (%)                              | 9 (3)                                     | 1 (<1)                                     | 7 (2)  |
| Fibrosis stage 5 — no. (%)                              | 20 (7)                                    | 24 (8)                                     | 14 (5)                                       |
| Fibrosis stage 6 — no. (%)                              | 15 (5)                                    | 20 (7)                                     | 21 (7)                                       |
| Hemophilia and cirrhosis — no. (%)¶                     | 1 (<1)                                    | 0  | 2 (1)  |
| Antiretroviral therapy — no. (%)                        |   |  |  |
| Any   | 240 (84)                                  | 243 (85)                                   | 244 (84)                                     |
| Nucleoside reverse-transcriptase inhibitors             | 239 (84)                                  | 240 (84)                                   | 243 (84)                                     |
| Nonnucleoside reverse-transcriptase inhibitors          | 99 (35)                                   | 104 (36)                                   | 102 (35)                                     |
| Protease inhibitors                                     | 128 (45)                                  | 133 (47)                                   | 123 (43)                                     |
| HIV-1 RNA   |   |  |  |
| Mean — log <sub>10</sub> copies/ml                      | 2.3±1.0                                   | 2.4±1.0                                    | 2.3±1.0                                      |
| Undetectable HIV RNA (<50 copies/ml) — no. (%)          | 170 (60)                                  | 171 (60)                                   | 173 (60)                                     |
| CD4+ cells — no./mm <sup>3</sup>                        |   |  |  |
| Mean  | 542±270                                   | 530±265                                    | 520±277                                      |
| <200/mm <sup>3</sup> — no. (%)                          | 20 (7)                                    | 14 (5)                                     | 17 (6)                                       |

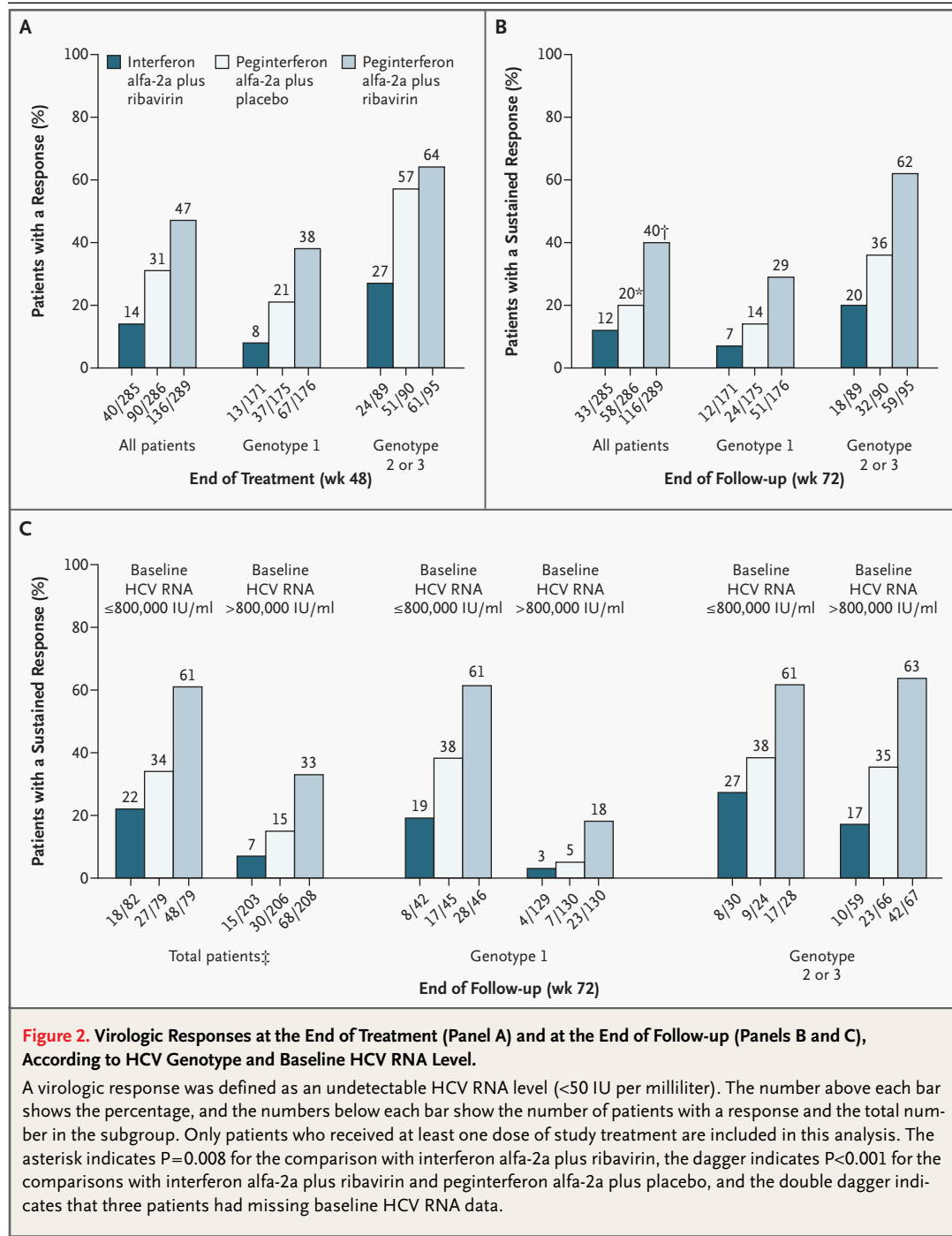
\* Plus-minus values are means ±SD.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The alanine aminotransferase quotient is the patient's level divided by the upper limit of normal.

§ Baseline liver-biopsy specimens were assessed by local pathologists using the Ishak Modified Histological Activity Index scoring system.<sup>10</sup>

¶ Cirrhosis was detected by magnetic resonance imaging or ultrasonography.



the three groups; however, the rate of dose reductions in response to laboratory abnormalities varied according to the treatment (Table 2). Grade 4 neutropenia (<500 cells per cubic millimeter) occurred in 1 recipient of interferon alfa-2a plus ribavirin (<1 percent), 37 recipients of peginterferon alfa-2a plus placebo (13 percent), and 31 recipients

of peginterferon alfa-2a plus ribavirin (11 percent). Grade 4 thrombocytopenia (<20,000 cells per cubic millimeter) occurred in one recipient of peginterferon alfa-2a plus placebo and one recipient of peginterferon alfa-2a plus ribavirin. Grade 4 anemia (hemoglobin level, <6.5 g per deciliter) occurred in five recipients of peginterferon alfa-2a

plus placebo (2 percent) and two recipients of peginterferon alfa-2a plus ribavirin (1 percent). Two patients withdrew from treatment with interferon alfa-2a plus ribavirin, three from treatment with peginterferon alfa-2a plus placebo, and two from treatment with peginterferon alfa-2a plus ribavirin because of anemia; one, seven, and four, respectively, withdrew because of thrombocytopenia, and none, two, and three because of neutropenia.

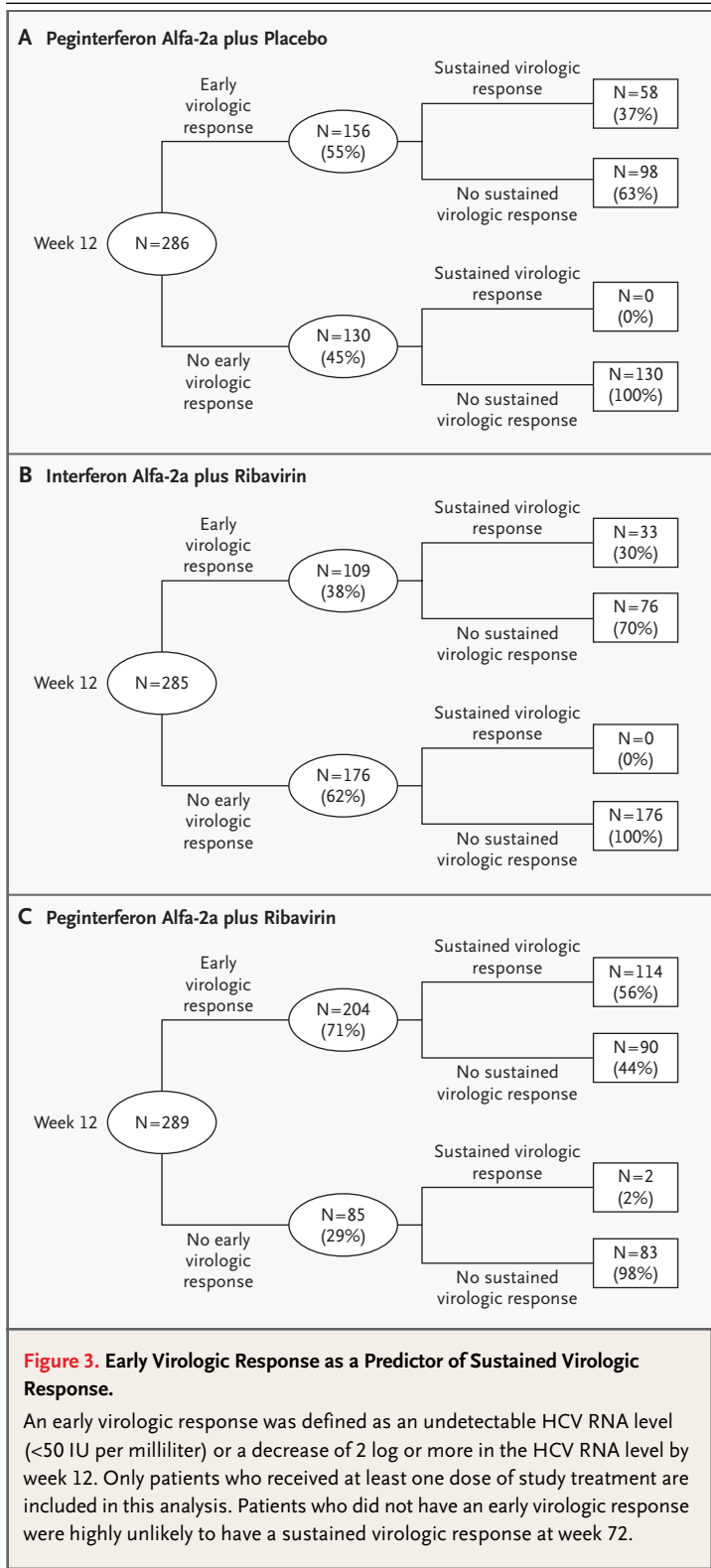
The proportion of patients withdrawn from treatment differed among treatment groups (Fig. 1 and Table 2). Overall, 39 percent of patients withdrew from treatment with interferon alfa-2a plus ribavirin, 31 percent from treatment with peginterferon alfa-2a plus placebo, and 25 percent from treatment with peginterferon alfa-2a plus ribavirin ( $P < 0.001$  for the comparison between interferon alfa-2a plus ribavirin and peginterferon alfa-2a plus ribavirin). The number of patients reporting adverse events or serious adverse events was generally similar among the treatment groups; serious events judged to be related to treatment were more frequent in the two groups that received peginterferon alfa-2a (Table 2).

Absolute mean CD4+ cell counts decreased uniformly in all three groups during treatment, whereas the mean percentage of CD4+ lymphocytes (CD4+ percentage) increased slightly (Table 2). Mean HIV-1 RNA levels decreased in patients treated with peginterferon alfa-2a who had detectable HIV RNA at baseline. Ten AIDS-defining events occurred during the study; these were evenly distributed among the three groups.

The incidence of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis was low (Table 2). Hepatic decompensation occurred in 14 of the 860 patients who received at least one dose of study medication and was evenly distributed among the treatment groups. All 14 patients had cirrhosis and Child–Pugh scores of 5 or higher at baseline; 6 of the 14 died.<sup>12</sup> Ten deaths occurred during the study, and two after the end of treatment and follow-up (Table 2). The death of one patient who received interferon alfa-2a plus ribavirin, attributed to respiratory failure, and of one who received peginterferon alfa-2a plus ribavirin, attributed to suicide, were judged to be possibly related to treatment.

DISCUSSION

In this large, randomized, placebo-controlled trial, peginterferon alfa-2a plus ribavirin elicited signifi-



**Table 2. Patients Withdrawn from Study Treatment, Dose Reductions, Adverse Events, and Changes in HIV Status According to Treatment Group.\***

| Variable   | Interferon Alfa-2a plus Ribavirin (N=285) |           | Peginterferon Alfa-2a plus Placebo (N=286) |         | Peginterferon Alfa-2a plus Ribavirin (N=288) |           |
|--|---|-----------|--|---------|--|-----------|
|  | number of patients (percent)              |           |  |         |  |           |
| <b>Withdrawal from study treatment</b>                         |   |           |  |         |  |           |
| Any reason   | 111 (39)†                                 |           | 90 (31)                                    |         | 72 (25)                                      |           |
| Adverse events or intercurrent illness                         | 41 (14)                                   |           | 34 (12)                                    |         | 34 (12)                                      |           |
| Insufficient response  | 34 (12)                                   |           | 14 (5)                                     |         | 6 (2)  |           |
| Patient's refusal of treatment                                 | 18 (6)                                    |           | 9 (3)                                      |         | 12 (4)                                       |           |
| Laboratory abnormalities‡                                      | 3 (1)                                     |           | 13 (5)                                     |         | 9 (3)  |           |
| Loss to follow-up  | 12 (4)                                    |           | 12 (4)                                     |         | 7 (2)  |           |
| Other  | 3 (1)                                     |           | 8 (3)                                      |         | 4 (1)  |           |
|  | Interferon Alfa-2a                        | Ribavirin | Peginterferon Alfa-2a                      | Placebo | Peginterferon Alfa-2a                        | Ribavirin |
| <b>Reduction or omission of one or more doses</b>              |   |           |  |         |  |           |
| Due to adverse event   | 33 (12)                                   | 62 (22)   | 21 (7)                                     | 66 (23) | 30 (10)                                      | 71 (25)   |
| Due to any laboratory abnormality                              | 18 (6)                                    | 34 (12)   | 94 (33)                                    | 33 (12) | 97 (34)                                      | 53 (18)   |
| Anemia   | 3 (1)                                     | 32 (11)   | 5 (2)                                      | 18 (6)  | 4 (1)  | 46 (16)   |
| Neutropenia  | 8 (3)                                     | 0         | 77 (27)                                    | 8 (3)   | 79 (27)                                      | 3 (1)     |
| Thrombocytopenia   | 4 (1)                                     | 0         | 21 (7)                                     | 7 (2)   | 18 (6)                                       | 4 (1)     |
| Other  | 4 (1)                                     | 2 (1)     | 9 (3)                                      | 2 (1)   | 7 (2)  | 2 (1)     |
|  | Interferon Alfa-2a plus Ribavirin (N=285) |           | Peginterferon Alfa-2a plus Placebo (N=286) |         | Peginterferon Alfa-2a plus Ribavirin (N=288) |           |
| <b>At least one treatment with hematopoietic growth factor</b> |   |           |  |         |  |           |
| Erythropoietin   | 12 (4)                                    |           | 14 (5)                                     |         | 30 (10)                                      |           |
| Granulocyte colony-stimulating factor                          | 4 (1)                                     |           | 35 (12)                                    |         | 34 (12)                                      |           |
| <b>At least one adverse event</b>                              |   |           |  |         |  |           |
| Any adverse event  | 273 (96)                                  |           | 271 (95)                                   |         | 276 (96)                                     |           |
| Serious adverse events   | 44 (15)                                   |           | 59 (21)                                    |         | 50 (17)                                      |           |
| Treatment-related serious adverse events§                      | 15 (5)                                    |           | 28 (10)                                    |         | 24 (8)                                       |           |
| <b>Death</b>   |   |           |  |         |  |           |
| Total  | 3   |           | 5  |         | 4  |           |
| Treatment-related¶   | 1   |           | 0  |         | 1  |           |
| <b>Specific adverse events  </b>                               |   |           |  |         |  |           |
| Fatigue  | 115 (40)                                  |           | 117 (41)                                   |         | 128 (44)                                     |           |
| Pyrexia  | 101 (35)**                                |           | 123 (43)                                   |         | 128 (44)                                     |           |
| Headache   | 117 (41)                                  |           | 110 (38)                                   |         | 111 (39)                                     |           |
| Myalgia  | 82 (29)                                   |           | 94 (33)                                    |         | 103 (36)                                     |           |
| Nausea   | 70 (25)                                   |           | 78 (27)                                    |         | 85 (30)                                      |           |
| Diarrhea   | 68 (24)                                   |           | 73 (26)                                    |         | 81 (28)                                      |           |
| Insomnia   | 84 (29)                                   |           | 61 (21)                                    |         | 76 (26)                                      |           |
| Asthenia   | 67 (24)                                   |           | 64 (22)                                    |         | 82 (28)                                      |           |
| Depression   | 64 (22)                                   |           | 57 (20)                                    |         | 76 (26)                                      |           |

cantly higher rates of sustained virologic response than interferon alfa-2a plus ribavirin in patients infected with both HIV and HCV (40 percent vs. 12 percent,  $P < 0.001$ ). These data are consistent with published results from a study of patients with HCV infection but without HIV infection.<sup>7</sup> Peginterferon alfa-2a monotherapy was also significantly more

effective than interferon alfa-2a plus ribavirin in our study (rate of sustained virologic response, 20 percent vs. 12 percent;  $P = 0.008$ ), a finding that suggests that peginterferon alfa-2a monotherapy is a suitable alternative for patients who cannot tolerate or have a contraindication to ribavirin.

The 29 percent rate of sustained virologic re-

| <b>Table 2. (Continued.)</b>   |  |   |   |
|--|--|---|---|
| <b>Variable</b>  | <b>Interferon Alfa-2a plus Ribavirin (N=285)</b> | <b>Peginterferon Alfa-2a plus Placebo (N=286)</b> | <b>Peginterferon Alfa-2a plus Ribavirin (N=288)</b> |
|  | <i>number of patients (percent)</i>              |   |   |
| <b>Specific serious adverse events††</b>                             |  |   |   |
| Lower respiratory tract infection                                    | 5 (2)  | 7 (2)   | 2 (1)   |
| Anemia   | 3 (1)  | 6 (2)   | 6 (2)   |
| Thrombocytopenia   | 0  | 4 (1)   | 1 (<1)  |
| Drug abuse   | 3 (1)  | 1 (<1)  | 4 (1)   |
| Lactic acidosis  | 0  | 4 (1)   | 1 (<1)  |
| Hepatic failure  | 2 (1)  | 3 (1)   | 1 (<1)  |
| Gastroenteritis  | 0  | 3 (1)   | 2 (1)   |
| Bacterial infection  | 1 (<1)   | 1 (<1)  | 3 (1)   |
| Pyrexia  | 1 (<1)   | 3 (1)   | 0   |
| Deep-vein thrombosis   | 0  | 0   | 3 (1)   |
| Lower-limb fracture  | 1 (<1)   | 3 (1)   | 0   |
| Nausea or vomiting   | 3 (1)  | 0   | 0   |
| Hepatic decompensation‡‡   | 4 (1)  | 5 (2)   | 5 (2)   |
| <b>Pancreatitis, symptomatic hyperlactatemia, or lactic acidosis</b> |  |   |   |
| Pancreatitis   | 1 (<1)   | 4 (1)   | 2 (1)   |
| Symptomatic hyperlactatemia  | 2 (1)  | 0   | 4 (1)   |
| Lactic acidosis  | 1 (<1)   | 4 (1)   | 2 (1)   |
| AIDS-defining event§§  | 3 (1)  | 3 (1)   | 4 (1)   |
|  | <i>mean ± SD (no. of patients)</i>               |   |   |
| <b>Changes in HIV disease status¶¶</b>                               |  |   |   |
| <b>Change in CD4+ count</b>  |  |   |   |
| Cells/mm <sup>3</sup>  | -131±176 (161)                                   | -135±173 (176)                                    | -157±176 (203)                                      |
| Percentage   | +1.3±5.9 (123)                                   | +1.4±6.3 (135)                                    | +3.0±8.2 (160)                                      |
| <b>Change in HIV-1 RNA — log<sub>10</sub> copies/ml</b>              |  |   |   |
| All patients   | +0.088±0.726 (163)                               | -0.219±0.925 (173)                                | -0.205±0.831 (204)                                  |
| Patients with detectable HIV-1 RNA at baseline                       | +0.016±1.010 (56)                                | -0.789±1.013 (67)                                 | -0.696±0.924 (82)                                   |

\* Data on withdrawals and deaths are based on all patients who underwent randomization and received at least one dose of study medication. One patient received peginterferon alfa-2a plus ribavirin but did not return for a safety assessment. All other analyses included all patients who underwent randomization, received at least one dose of study medication, and had at least one safety evaluation after baseline.

† P<0.001 for the comparison with peginterferon alfa-2a plus ribavirin by Fisher's exact test.

‡ Laboratory abnormalities leading to premature withdrawal from study treatment included anemia, lymphopenia, neutropenia, thrombocytopenia, increased aminotransferase levels, and increased creatine kinase levels.

§ In the opinion of the investigator, these events were judged to be possibly or probably related to the study treatment.

¶ Among patients treated with interferon alfa-2a plus ribavirin, one patient each died from nosocomial pneumonia and enterococcal bacteremia, hepatic failure, and respiratory failure. Among patients treated with peginterferon alfa-2a plus placebo, two deaths were attributed to hepatic failure and one each to hepatitis C, upper gastrointestinal hemorrhage, and anoxic encephalopathy. Among patients treated with peginterferon alfa-2a plus ribavirin, the four deaths were attributed to upper gastrointestinal hemorrhage, hepatic encephalopathy, metastatic carcinoma, and suicide.

|| The adverse events listed are those that occurred in at least 25 percent of patients in at least one treatment group, regardless of the relationship to treatment.

\*\* P=0.03 for the comparison with peginterferon alfa-2a plus ribavirin by Fisher's exact test.

†† The adverse events listed are those that occurred in at least three patients (1 percent) in at least one treatment group, regardless of the relationship to treatment. Serious adverse events were defined as fatal or life-threatening events and those that required or prolonged hospitalization, resulted in persistent or clinically significant disability or congenital anomaly, or required intervention to prevent one of the specific serious adverse events just listed.

‡‡ Among those with hepatic decompensation, the number of patients with baseline Child-Pugh scores of 5, 6, and 7 or more were as follows: interferon alfa-2a plus ribavirin, 2, 0, and 2; peginterferon alfa-2a plus placebo, 1, 1, and 3; peginterferon alfa-2a plus ribavirin, 1, 2, and 2, respectively.

§§ Among the 10 AIDS-defining events, there were six cases of esophageal candidiasis, two cases of herpes zoster (one each in recipients of interferon alfa-2a plus ribavirin and peginterferon alfa-2a plus ribavirin), and two presumptive cases of progressive multifocal leukoencephalopathy (one each in recipients of interferon alfa-2a plus ribavirin and peginterferon alfa-2a plus ribavirin).

¶¶ Values shown are mean (±SD) changes from baseline at 48 weeks, with the number of patients shown in parentheses. Only patients who received 48 weeks of treatment are included. CD4+ percentage indicates percentage of CD4+ lymphocytes.

||| Detectable levels were ≥50 copies per milliliter.

sponse in patients infected with HCV genotype 1 who were treated with peginterferon alfa-2a plus ribavirin is higher than the rates previously reported in patients coinfecting with HIV and HCV. In the two groups that received ribavirin, relapse rates, indicated by the difference between responses at the end of treatment and responses at the end of follow-up, were remarkably low and similar to those in patients infected only with HCV, underscoring the importance of ribavirin in viral clearance.<sup>13</sup> The highest response rate was among patients with HCV genotype 2 or 3 who received peginterferon alfa-2a plus ribavirin. The similar responses at the end of treatment (48 weeks) and the end of follow-up in our trial (72 weeks) — 64 percent and 62 percent — contrast with the high relapse rate (35 percent) reported after 24 weeks of treatment in another trial.<sup>14</sup> Thus, although patients infected only with HCV genotype 2 or 3 require only 24 weeks of treatment,<sup>6</sup> 48 weeks of combination therapy appears to be appropriate for patients infected with both HIV and HCV genotype 2 or 3.

Although outcomes according to HCV genotype and pretreatment HCV RNA level are consistent with previously published data, the rates of sustained virologic response in our trial were generally lower than those reported for patients with HCV infection alone.<sup>7</sup> Several factors may contribute to this finding. First, more than 70 percent of our subjects had high pretreatment HCV RNA titers (>800,000 IU per milliliter). Second, the viral kinetic response to anti-HCV therapy is slower in patients infected with HCV and HIV.<sup>15</sup> Although our study population was relatively immunocompetent, as reflected by their absolute CD4+ counts, some as yet unrecognized qualitative defects in immune function might also have affected their ability to eradicate HCV. Finally, we used a fixed, 800-mg daily dose of ribavirin. In patients with HCV infection alone, a recent trial showed that even higher doses of ribavirin (1000 or 1200 mg per day) resulted in better rates of sustained virologic response in patients infected with HCV genotype 1.<sup>6</sup> This finding provides a rationale for the use of a higher initial dose of ribavirin in future studies.

Patients who did not have an early virologic response at week 12 were highly unlikely to have a sustained virologic response. The negative predictive value of the absence of an early response was not improved when such a response was defined as occurring by week 24. Thus, in accordance with current guidelines for HCV-infected patients with-

out HIV coinfection, discontinuation of therapy can be considered if patients do not have a virologic response by week 12.<sup>5</sup>

The spectrum and frequency of adverse events were similar to those previously reported in HCV infection.<sup>7</sup> Hematologic abnormalities were more frequent among patients treated with peginterferon alfa-2a. The overall frequency of AIDS-defining events and of death, as well as events associated with mitochondrial toxicity, such as pancreatitis and lactic acidosis, was low, and it was similar among the treatment groups. Although combination therapy was associated with a decline in absolute CD4+ cell counts, it had no effect on the CD4+ percentage. Notably, mean HIV RNA levels did not increase during treatment with peginterferon alfa-2a and, in fact, decreased by approximately 0.7 log<sub>10</sub> copy in patients who had detectable HIV-1 RNA at baseline.

The overall rate of sustained virologic response among patients treated with peginterferon alfa-2a plus ribavirin (40 percent, as compared with 12 percent for those treated with interferon alfa-2a plus ribavirin) was considerably higher than that in other recent trials of peginterferon and ribavirin in patients with both HIV and HCV infection.<sup>16,17</sup> In the AIDS Clinical Trials Group A5071 study,<sup>16</sup> the rates of sustained virologic response were 27 percent with peginterferon alfa-2a plus ribavirin and 12 percent with interferon alfa-2a plus ribavirin. The rates of sustained virologic response were similar in a French multicenter study that compared peginterferon alfa-2b plus ribavirin with interferon alfa-2b plus ribavirin (26 percent vs. 18 percent).<sup>17</sup> Although the results must be interpreted with caution, there are several possible reasons for the better responses observed in our trial. These include differences in study design, the use of a different type of peginterferon in one study<sup>17</sup> and a different dose of ribavirin in the other,<sup>16</sup> and differences in patient populations.

In conclusion, our results demonstrate that the current regimen used for the treatment of chronic hepatitis C alone can also be applied to patients coinfecting with HIV and HCV. Peginterferon alfa-2a plus ribavirin has a favorable risk-to-benefit ratio when used to treat such patients, a substantial proportion of whom are likely to benefit from therapy with this combination.

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#### APPENDIX

In addition to the authors, the members of the APRICOT study group were as follows: A. Alaeus, Karolinska Institute, Stockholm; A. Allworth, Royal Brisbane Hospital, Herston, Queensland, Australia; M.M. Andrews, Dartmouth Medical School, Lebanon, N.H.; F. Antunes, Clinica de Doencas Infecciosas, Hospital de Santa Maria, Lisbon; J. Arrizabalaga, Hospital Nuestra Senora de Aranzazu, San Sebastian, Spain; L. Balart, Louisiana State University Health Science Center, New Orleans; E. Barranco, R. Baumgarten, Krankenhaus Prenzlaue Berg II, Berlin; M. Beaman, University of Western Australia, Crawley, Australia; M. Borucki, University of Texas Health Center at Tyler; E. Bouza, Hospital Gregorio Maranon, Madrid; N. Bräu, Bronx Veterans Affairs Medical Center, Bronx, N.Y.; P. Buggisch, Universitätsklinik, Hamburg, Germany; G. Cadeo, Spedali Civili-Brescia, Brescia, Italy; P. Cahn, Fundacion Huesped, Buenos Aires; I. Cassetti, Fundacion Centro de Estudios Infectologicos, Buenos Aires; B. 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Godofsky, Bach and Godofsky, Bradenton, Fla.; F. Goncalves, Universidade Estadual de Campinas Hospital das Clinicas, Campinas, Brazil; P. Greiger, Mt. Vernon Hospital, Mt. Vernon, N.Y.; J. Guardiola, Hospital Santa Creu i Sant Pau, Barcelona, Spain; E. Guzman, B. Hirschel, Hôpital Cantonal Universitaire de Genève, Geneva; I.M. Hoepelman, University Medical Center, Utrecht, the Netherlands; R. Kalayjian, University Hospital of Cleveland, Cleveland; N. Khardori, Southern Illinois School of Medicine, Springfield; R. Koff, University of Massachusetts Memorial Health Care, Chestnut Hill; J. Lalezari, HIV Research Center, Mt. Zion Hospital, University of California, San Francisco; H. Lecour, School of Medicine, Hospital de São Joao, Porto, Portugal; C. Leen, Western General Hospital, Edinburgh; K. Lindsay, University of Southern California, Los Angeles; A. Maeland, J. Main, St. Mary's Hospital, London; G. Marinos, Prince of Wales Hospital, Sydney; N. Markowitz, Henry Ford Hospital, Detroit; F. Mazzotta, S.M. Annunziata Hospital, Florence, Italy; B. McGovern, New England Medical Center, Boston; J.-L. Meynard, Hôpital Saint Antoine, Paris; J.-M. Molina, Hôpital Saint-Louis, Paris; S. Moreno, Hospital Ramón y Cajal, Madrid; M. Nelson, Chelsea and Westminster Hospital, London; M. Opravil, University Hospital Zurich, Zurich, Switzerland; E. Ortega, Hospital General Universitario de Valencia, Valencia, Spain; G. Pastore, Policlinico di Bari, Bari, Italy; C. Pedersen, Odense University Hospital, Odense, Denmark; G. Pialoux, Hôpital Rothschild, Paris; P. Piliro, Albany Medical College, Albany, N.Y.; J. Pocas, Hospital de São Bernardo, Setúbal, Portugal; K. Raben, Drs. Raben & Feldman Research Associates, Miami; R. Redfield, Institute of Human Virology, Baltimore; R. Reindollar, Carolinas Center for Liver Disease, Charlotte, N.C.; J. 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