A Randomized, Double-blind Trial Comparing Combinations of Nevirapine, Didanosine, and Zidovudine for HIV-Infected Patients

The INCAS Trial

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Context.—Current guidelines recommend that individuals infected with the human immunodeficiency virus type 1 (HIV-1) be treated using combinations of antiretroviral agents to achieve sustained suppression of viral replication as measured by the plasma HIV-1 RNA assay, in the hopes of achieving prolonged remission of the disease. However, until recently, many drug combinations have not led to sustained suppression of HIV-1 RNA.

Objective.—To compare the virologic effects of various combinations of nevirapine, didanosine, and zidovudine.

Design.—Double-blind, controlled, randomized trial.

Setting.—University-affiliated ambulatory research clinics in Italy, the Netherlands, Canada, and Australia (INCAS).

Patients.—Antiretroviral therapy–naive adults free of the acquired immunodeficiency syndrome with CD4 cell counts between 0.20 and 0.60 x 10^9/L (200-600/µL).

Intervention.—Patients received zidovudine plus nevirapine (plus didanosine placebo), zidovudine plus didanosine (plus nevirapine placebo), or zidovudine plus didanosine plus nevirapine.

Main Outcome Measure.—Plasma HIV-1 RNA.

Results.—Of the 153 enrolled patients, 151 were evaluable. At week 8, plasma HIV-1 RNA levels had decreased by log 2.18, 1.55, and 0.90 in the triple drug therapy, zidovudine plus didanosine, and zidovudine plus nevirapine groups, respectively (P<0.05). The proportions of patients with plasma HIV-1 RNA levels below 20 copies per milliliter at week 52 were 51%, 12%, and 0% in the triple drug therapy, zidovudine plus didanosine, and zidovudine plus nevirapine groups, respectively (P<0.001). Viral amplification was attempted in 59 patients at 6 months. Viral isolation was unsuccessful in 19 (79%) of 24, 10 (53%) of 19, and 5 (31%) of 16 patients in the triple drug therapy, zidovudine plus didanosine, and zidovudine plus nevirapine groups, respectively. Among patients from whom virus could be amplified, resistance to nevirapine was found in all 11 patients receiving zidovudine plus nevirapine and in all 5 patients receiving triple drug therapy. Rates of disease progression or death were 23% (11/47), 25% (13/53), and 12% (6/51) for the zidovudine plus nevirapine, zidovudine plus didanosine, and triple drug therapy groups, respectively (P<0.08).

Conclusions.—Triple drug therapy with zidovudine, didanosine, and nevirapine led to a substantially greater and sustained decrease in plasma viral load than the 2-drug regimens studied. Our results also suggest that suppression of viral replication, as demonstrated by a decrease in the plasma HIV-1 RNA load below the level of quantitation of the most sensitive test available, may at least forestall the development of resistance.

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For editorial comment see p 957.

Early clinical experience with nevirapine monotherapy demonstrated a substantial but transient decline of serum p24 antigen levels. The loss of nevirapine activity was temporally associ-
ated with the emergence of drug resistance. Similar transient benefits were demonstrated when zidovudine and nevirapine were used in an alternating schedule. Administration of nevirapine in combination with zidovudine alone or zidovudine plus didanosine in previously treated patients led to a substantial improvement in the magnitude and durability of the antiviral response. Nevertheless, the responses waned over time. Of note, the response seen with the triple drug therapy regimen was more durable, remaining beyond 1 year, particularly among patients with limited prior drug exposure.

We hypothesized that a more vigorous suppression of viral replication could prevent or delay the emergence of nevirapine resistance and ultimately prolong the effect of treatment. We therefore undertook the present study to compare the virologic and immunologic effects of various combinations of nevirapine, didanosine, and zidovudine among antiretroviral therapy-naive, HIV-1–infected patients free of the acquired immunodeficiency syndrome (AIDS).

METHODS
Study Design and Patients

This was a double-blind, controlled, randomized trial conducted in Italy, the Netherlands, Canada, and Australia (also known as the INCAS Trial). Patients were recruited from those evaluated at the university-affiliated ambulatory research clinics of each participating center starting on July 20, 1994. The last patient completed the intended 52-week follow-up on July 31, 1996. Consecutive individuals 18 years or older who had HIV-1 infection, CD4 cell counts between 0.20 and 0.60 × 10^9/L (200-600/μL), no prior AIDS-defining illnesses, and no prior exposure to antiretroviral medications were eligible. Exclusion criteria included absolute neutrophil count less than 1.0 × 10^9/L; platelet count less than 0.8 × 10^11/L; hemoglobin level less than 95 or 90 g/L for male and female patients, respectively; transaminase levels more than 3 times the upper limit of the normal range; bilirubin level more than 1.5 times the upper limit of the normal range; alkaline phosphatase level more than 2.5 times the upper limit of the normal range; serum creatinine level more than 1.5 times the upper limit of the normal range; Karnofsky score below 80; use of immunosuppressive, cytotoxic, or experimental therapy within 4 weeks of entry; presence of 4 or more stools per day; pregnant, breast-feeding, or unwilling to avoid pregnancy for the duration of the trial. The protocol and informed consent were approved by the institutional review boards of the participating centers.

Patients were randomly allocated to 3 intervention arms: zidovudine, nevirapine, zidovudine plus didanosine, or zidovudine plus didanosine plus nevirapine. Randomization was done at the coordinating center by country in blocks of 6 patients using a computer-generated random sequence. Third-party binding with identical didanosine and nevirapine placebos as appropriate was used to maintain the double-blind nature of the trial. Blind codes were kept at the study site’s pharmacy. There were no instances in which the blinding was broken during the study. Study medications were prescribed orally as currently recommended (nevirapine, 200 mg once daily for 2 weeks and 200 mg twice daily thereafter; zidovudine, 200 mg 3 times daily; and didanosine, 125 or 200 mg in mint-flavored tablets twice daily based on body weight).

Patients completed a screening visit within 1 month of starting to take study medications, and they were assessed again at baseline and on weeks 1, 2, and 4 and at 4-week intervals thereafter until week 52. Patients were evaluated at 8-week intervals after week 52 until all participants had completed 52 weeks in the study. At each visit, patients completed a clinical evaluation, a questionnaire eliciting potential adverse effects of study medications, and a laboratory assessment, including CD4 cell count and plasma HIV-1 RNA load.

Laboratory Tests

Absolute and percentage CD4 lymphocyte counts were obtained by flow cytometry at the institutional laboratories on a real-time basis. Plasma HIV-1 RNA load was determined by batch testing at the Clinical Retrovirology Laboratory of the British Columbia Centre for Excellence in HIV/AIDS, St Paul’s Hospital, University of British Columbia (Vancouver). Assays were performed using the Amplicor HIV Monitor Assay (Roche Diagnostics, Mississauga, Ontario), with a limit of quantitation of 400 copies per milliliter. Samples with less than 500 copies per milliliter were retested using the Ultra Direct Assay (Roche Molecular Systems, Alameda, Calif), with a limit of quantitation of 20 copies per milliliter. HIV phenotypic resistance was examined at 6 months in the European patients using a modification of the recombinant method of Kellam and Larder at VIRCO Laboratories (Mechelen, Belgium). The threshold for decreased susceptibility (increase in IC50) to a drug was defined as an increase greater than 5-fold in the inhibitory concentration of 50% for the test recombinant virus compared with the concurrent control wild-type virus. The maximum limit of the test was at an inhibitory concentration of 50% of 100 μmol/L.

Statistics

The estimated sample size was 120 patients, to allow for greater than 90% power to detect a difference of 0.75 SD between treatment regimens at a 2-sided a value of .05. Target enrollment was set at 150 patients to ensure that there would be 120 evaluable patients.

The primary end point of the study was the effect of study treatments on plasma HIV-1 RNA load and CD4 cell count over time. Baseline values were calculated as the arithmetic mean of the day 0 value and a pretreatment observation other than the screening value. The plasma HIV-1 RNA load was log transformed. The end-of-trial average measurement was derived from the average of results obtained at weeks 40, 44, 48, and 52 of the study. This was decided prior to the unblinding of the data to maximize the precision of the end-point measure. Analyses were completed on an intent-to-treat basis. All patients who had observations after initiation of the study treatment were included in the analyses. The average daily change from baseline was also measured for CD4 cell count and plasma HIV-1 RNA levels. This was also frequently referred to as “area under the curve minus baseline.” Change from baseline was used for the primary analyses. The plasma HIV-1 RNA load for each visit was determined using the Amplicor HIV Monitor Assay results for samples with 500 copies or more per milliliter and the Ultra Direct Assay results for samples with 20 to 500 copies per milliliter. In planned, standard analyses, analysis of variance models were applied, including terms for country, treatment, and their interaction. For pairwise comparisons of treatments, the F value for comparison of least-square means was applied. In additional efficacy analyses, patients were categorized according to their compliance with trial medications. Compliance was assessed based on patient-reported missed doses, as recorded in the case report form. Failure to take any dose of 1 or more of the active medications for a total of 28 or more consecutive or nonconsecutive days during the 52-week trial period was defined as noncompliance in this analysis.

Disease progression events were prospectively evaluated by the investigators, who remained blind with regard to the patient’s treatment allocation. Adverse events are reported according to the number of patients who experienced them. If a patient reported a specific event more
than once, the event with the worst severity assessment was included. The relationship of the adverse event to the study medications was judged by the investigator. Laboratory data were evaluated using the criteria of Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Laboratory abnormalities reported include any new grade III or IV abnormality or, if the grade at baseline was less than grade I, a grade II abnormality.

### RESULTS

#### Characteristics of the Study Patients

Of the 153 subjects enrolled, 2 failed to start taking the study medications and therefore were excluded from all analyses (Table 1). Of the 151 evaluable patients, 47 received zidovudine plus nevirapine, 53 received zidovudine plus didanosine, and 51 received triple drug therapy. As shown in Table 2, there were no statistically significant differences among the 3 treatment groups at base-

### Table 1.—Profile of the INCAS Trial (N = 153)*

<table>
<thead>
<tr>
<th>No. of Participants</th>
<th>Zidovudine Plus Nevirapine</th>
<th>Zidovudine Plus Didanosine</th>
<th>Zidovudine Plus Didanosine Plus Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received therapy</td>
<td>47</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Did not receive therapy</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Followed up</td>
<td>47</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>With CD4 cell count data</td>
<td>47</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>With RNA data</td>
<td>46</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Withdraw</td>
<td>20</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Due to adverse event</td>
<td>12</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unavailable for follow-up</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Completed 52 wk of trial, No. (%)</td>
<td>27 (57)</td>
<td>35 (66)</td>
<td>37 (73)</td>
</tr>
</tbody>
</table>

*One hundred fifty-three patients were enrolled. One patient was never randomized, 1 patient who was randomized never received drug therapy. INCAS indicates Italy, the Netherlands, Canada, Australia.

### Table 2.—Baseline Characteristics*†

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Zidovudine Plus Nevirapine</th>
<th>Zidovudine Plus Didanosine</th>
<th>Zidovudine Plus Didanosine Plus Nevirapine</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>37.8 (9)</td>
<td>36.4 (8.1)</td>
<td>38.0 (10.7)</td>
<td>.58</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>76.8 (11)</td>
<td>74.6 (13.3)</td>
<td>77.5 (11.6)</td>
<td>.28</td>
</tr>
<tr>
<td>Karnofsky score, No. (%)</td>
<td>80</td>
<td>65</td>
<td>82</td>
<td>.86</td>
</tr>
<tr>
<td>Disease stage, No. (%)</td>
<td>100</td>
<td>77</td>
<td>71</td>
<td>.80</td>
</tr>
<tr>
<td>CDC I</td>
<td>45 (96)</td>
<td>51 (96)</td>
<td>50 (98)</td>
<td></td>
</tr>
<tr>
<td>CDC II</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 cell count, ×10^3/L</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>.11</td>
</tr>
<tr>
<td>Mean</td>
<td>0.346</td>
<td>0.390</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.345</td>
<td>0.380</td>
<td>0.395</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.200-0.610</td>
<td>0.145-0.755</td>
<td>0.185-0.610</td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-1 RNA, log copies/mL‡</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.54</td>
<td>4.47</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.69</td>
<td>4.51</td>
<td>4.25</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2.85-5.86</td>
<td>2.50-5.62</td>
<td>2.84-5.56</td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-1 RNA, copies/mL¶</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>34,854</td>
<td>30,037</td>
<td>17,224</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>48,654</td>
<td>32,163</td>
<td>17,732</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*CDC indicates Centers for Disease Control and Prevention; HIV-1, human immunodeficiency virus type 1.
†For comparisons across the 3 treatment groups.
‡Eq 20 copies per milliliter.

**The maximal effect in the triple drug therapy group was observed at week 16, with 68% of patients demonstrating a plasma HIV-1 RNA level below 20 copies per milliliter.**

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24% [9/38] for zidovudine and 21% [8/38] for nevirapine. Drug-specific rates of noncompliance were 33% (34/104) for didanosine, 15% (23/151) for zidovudine, and 15% (15/98) for nevirapine (P = .02). These figures also allow for evaluation of the relationship between plasma viral load at baseline and response to treatment. Although the triple drug therapy group had a lower plasma viral load at baseline, virologic responses occurred in this group across the range of baseline plasma viral load. Similarly, lack of virologic response was observed in the 2-drug therapy groups across the range of baseline plasma viral load.

Table 4 summarizes the results of the resistance studies conducted in a subset of 59 European and Australian patients at 6 months. Among them, virus could not be amplified by the VIRCO Laboratories assay in 5 (31%) of 16, 10 (53%) of 19, and 19 (79%) of 24 patients in the zidovudine plus nevirapine, zidovudine plus didanosine, and triple drug therapy groups, respectively. Resistance to zidovudine occurred in 4 (21%), 1 (6%), and 0 patients in the zidovudine plus didanosine, zidovudine plus nevirapine, and triple drug therapy groups, respectively. Among patients from whom virus could be amplified, resistance to nevirapine was detected in all 11 and all 5 patients in the zidovudine plus nevirapine and triple drug therapy groups, respectively. Of interest, all but 1 of the nevirapine-treated patients with resistance in the triple drug therapy group were noncompliant. Resistance to didanosine or zidovudine was found in the triple drug therapy group regardless of compliance.

Immunologic Effect

As shown in Figure 4, all 3 treatments produced a rapid increase in mean absolute CD4 cell count. Mean CD4 cell counts remained more than 0.125 × 10^9/L above baseline at week 52 in patients receiving triple drug therapy. Changes in absolute CD4 cell count from baseline to the end of year average were 0.139 × 10^9/L (SE, 0.020 × 10^9/L), 0.087 × 10^9/L (0.021 × 10^9/L), and −0.006 × 10^9/L (0.024 × 10^9/L) for triple drug therapy, zidovudine plus didanosine, and zidovudine plus nevirapine, respectively. There was a 0.052 × 10^9/L difference in favor of triple drug therapy compared with zidovudine plus didanosine (P = .03).

Disease Progression Events and Death

A total of 31 patients had disease progression or died during the study. There

Table 3.—Plasma HIV-1 RNA Levels Below the Limit of Quantification From Weeks 40 to 52

<table>
<thead>
<tr>
<th>Plasma HIV-1 RNA Level, Copies/mL</th>
<th>Zidovudine Plus Nevirapine (Group 1) (n = 28)</th>
<th>Zidovudine Plus Didanosine (Group 2) (n = 36)</th>
<th>Zidovudine Plus Didanosine Plus Nevirapine (Group 3) (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>0</td>
<td>6 (22)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>0</td>
<td>4 (11)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>0</td>
<td>2 (6)</td>
<td>18 (45)</td>
</tr>
</tbody>
</table>

P†

Group 2 vs Group 3: .004 < .001
Group 2 vs Group 1: .004 < .001
Group 1 vs Group 3: .001 < .001

†Cochran-Mantel-Haenszel test, adjusting for country.
were 2 deaths, 1 in each of the 2-drug therapy groups. As shown in Table 5, most of the disease progression events were caused by non–AIDS defining diseases (Centers for Disease Control and Prevention group B). Rates of disease progression or death were 23% (11/47), 25% (13/53), and 12% (6/51) for the zidovudine plus nevirapine, zidovudine plus didanosine, and the triple drug therapy groups, respectively. There was a trend toward a lower rate of disease progression in the triple drug therapy group compared with the zidovudine plus didanosine group ($P = .08$).

### Adverse Events

Table 6 summarizes the adverse events that were judged by the investigators to be possibly related to 1 or more of the study medications (or placebo) and that occurred in at least 10% of patients in at least 1 of the treatment arms. Gastrointestinal complaints were the most frequently identified adverse events for all treatment groups. These were the events that led most frequently to the discontinuation of zidovudine (20/151 [13%]), didanosine (23/104 [22%]), and nevirapine (10/98 [10%]) therapy. Treatment-related rash occurred in 22 (22%) of 98 patients in the nevirapine treatment arms vs 3 (6%) of 53 patients in the zidovudine plus didanosine treatment arm ($P = .01$). Severe rash developed in 4 (4%) of 98 patients in the nevirapine groups compared with 1 (2%) of 53 patients in the zidovudine plus didanosine group ($P = .85$). The remainder of the rashes were mild to moderate, and there were no episodes of Stevens-Johnson syndrome.

The most frequent laboratory test abnormalities were elevated $\gamma$-glutamyltransferase (17% [26/151]), alanine aminotransferase (14% [21/151]), creatine phosphokinase (12% [18/151]), aspartate aminotransferase (11% [17/151]), amylase (7% [11/151]), total bilirubin (4% [6/151]), and hemoglobin (1% [2/151]) levels and decreased neutrophil count (5% [7/151]). Overall, 26 (27%) of 98 patients treated with nevirapine developed at least 1 laboratory test abnormality, compared with 6 (11%) of the 53 patients treated with zidovudine plus didanosine ($P = .04$). Elevated liver function test results were seen in 14 (30%) of 47 patients in the nevirapine plus zidovudine group, in 12 (24%) of 51 patients in the nevirapine plus zidovudine plus didano-
sine group, and in 6 (11%) of 53 patients in the zidovudine plus didanosine group. Five patients treated with nevirapine stopped taking the study medication permanently because of elevated alanine aminotransferase levels. In all cases, alanine aminotransferase levels normalized after the patients stopped taking nevirapine. Other laboratory abnormalities occurred with comparable frequency in each treatment group.

**COMMENT**

Our results demonstrate that triple drug therapy with zidovudine plus didanosine plus nevirapine led to a substantially greater decrease in plasma viral load and increase in CD4 cell count than the 2-drug regimens over 1 year among antiretroviral therapy-naive, AIDS-free, HIV-1-infected adults with baseline CD4 cell counts between 0.20 and 0.60 × 10^9/L. Our results also suggest that suppression of viral replication, as demonstrated by a decrease in plasma viral load below the level of quantitation of the most sensitive test available, can forestall if not prevent the emergence of resistance.

The role of nevirapine in the treatment of HIV infection has been previously explored in surrogate marker trials. deJong et al reported on the effects of an alternating regimen of 1 week of nevirapine and 3 weeks of zidovudine among antiretroviral therapy-naive, HIV-infected patients with detectable serum p24 antigen. In this pilot study, serum p24 antigen levels declined during the first week of nevirapine treatment; however, subsequent courses of nevirapine were characterized by rising serum p24 antigen levels, attributed to the development of nevirapine resistance. In another study, Carr et al randomized asymptomatic HIV-1–infected patients with CD4 cell counts of 0.20 to 0.50 × 10^9/L who had 3 to 24 months of prior zidovudine therapy to receive zidovudine monotherapy or zidovudine plus nevirapine. Combination therapy was associated with an initial decrease in plasma HIV-1 RNA levels greater than 1.5 log copies per milliliter in the triple and double therapy arms, respectively. Again, these values tended to return toward baseline after continued therapy. In contrast, our data for the first time demonstrate that simultaneous introduction of zidovudine, didanosine, and nevirapine in antiretroviral therapy–naive patients can result in substantial and sustained benefit. This is consistent with the results of a recent exploratory analysis conducted within the ACTG 241 protocol, in which a better virologic response to therapy was reported among patients with limited prior exposure to antiretroviral agents and CD4 cell counts greater than 0.20 × 10^9/L. These data suggest that nevirapine should be used within a highly suppressive regimen. Conversely, these data indicate that nevirapine should not be recommended as part of a partially suppressive regimen, such as zidovudine plus nevirapine.

The use of zidovudine plus didanosine as control treatment in our study is supported by the results of the Delta and ACTG 175 studies.17,18 In each case, improvements in short-term clinical outcome were associated with favorable changes in CD4 cell counts and plasma HIV-1 RNA levels.19,20 The reliability of rises in CD4 cell count and reductions in HIV-1 RNA levels as a result of treatment in predicting clinical benefit has now been confirmed in a number of trials, including the CAESAR (Canada, Australia, Europe, South Africa Research) trial and the ACTG 320 study.21,22 This has led to a revision of the current guidelines for the use of antiretroviral therapy.23,24 It is currently recommended that treatment should be initiated with a regimen consisting of 2 nucleoside agents plus a po-

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**Table 5.—Disease Progression and Deaths Among All Patients**

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>Zidovudine Plus Nevirapine (n = 47)</th>
<th>Zidovudine Plus Didanosine (n = 53)</th>
<th>Zidovudine Plus Didanosine Plus Nevirapine (n = 51)</th>
<th>Total (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hairy leukoplakia</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Oral candida</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Oral hairy leukoplakia and oral candida</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Herpes zoster virus infection</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oral hairy leukoplakia and herpes zoster virus infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oral candida and herpes zoster virus infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total, No. (%)</strong></td>
<td>11 (23)</td>
<td>13 (25)</td>
<td>6 (12)</td>
<td>30 (20)</td>
</tr>
</tbody>
</table>

*P = .08 by 2-sided Fisher exact test for zidovudine plus didanosine vs zidovudine plus didanosine plus nevirapine, comparing the number of patients experiencing predefined disease progression or death.

**Table 6.—Adverse Events Judged by the Investigators to Be at Least Possibly Related to Nevirapine, Occurring in at Least 10% of Treated Patients**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zidovudine Plus Nevirapine (n = 47)</th>
<th>Zidovudine Plus Didanosine (n = 53)</th>
<th>Zidovudine Plus Didanosine Plus Nevirapine (n = 51)</th>
<th>Nevirapine-Treated Patients (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>11 (23)</td>
<td>13 (25)</td>
<td>9 (18)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (30)</td>
<td>15 (29)</td>
<td>10 (20)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (19)</td>
<td>7 (13)</td>
<td>14 (27)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (13)</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Flulike</td>
<td>11 (23)</td>
<td>11 (21)</td>
<td>8 (16)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (66)</td>
<td>32 (60)</td>
<td>35 (69)</td>
<td>66 (67)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (30)</td>
<td>14 (27)</td>
<td>6 (12)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Abnormal liver function test results</td>
<td>9 (19)</td>
<td>3 (6)</td>
<td>6 (12)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (13)</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (21)</td>
<td>3 (6)</td>
<td>12 (24)</td>
<td>22 (22)</td>
</tr>
</tbody>
</table>
of the reduced-mass, orange-flavored formulation of didanosine. Furthermore, recent data suggest that full daily doses of didanosine and nevirapine may be prescribed as a single daily dose. Again, it is anticipated that this will substantially improve compliance.

The proportion of patients with no detectable HIV-1 RNA in the triple drug therapy group reached a maximum of 68% at week 16, declining to 51% at week 52. It is noteworthy that a similar trend was observed in the zidovudine plus didanosine group: 24% and 12% of patients had plasma HIV-1 RNA levels below 20 copies per milliliter at weeks 16 and 52. Continued follow-up of this cohort will permit us to characterize the long-term durability of this effect. Given the suppressive rather than curative nature of this treatment, it is anticipated that a substantial number of patients may have difficulty complying with the treatment on a long-term basis, and therefore the effect of treatment may wane over time.

Although the overall dropout rate in the trial was 34%, this is not unusual for 1-year trials of antiretroviral agents. It is noteworthy that a larger proportion of patients in the triple drug therapy group completed the intended follow-up. No unexpected toxic effects or severe adverse effects were encountered in our study.4,5,8,11,12 Rash and liver test abnormalities led to the discontinuation of nevirapine therapy in 7% and 5% of our study patients, respectively. We encountered no episodes of life-threatening rashes or Stevens-Johnson syndrome.

Finally, our results also illustrate the importance of maximizing the sensitivity of the test used to measure the effect of antiretroviral therapies on plasma HIV-1 RNA levels. It was only by using the Ultra Direct Assay, with a threshold of quantitation of 20 copies per milliliter, that we were able to fully appreciate the difference in the level of suppression of viral replication achieved when nevirapine was used in addition to zidovudine and didanosine.11,14 Specifically, only a minority of patients who reached a threshold of less than 400 copies per milliliter in the zidovudine plus didanosine arm reached the more stringent criterion of less than 20 copies per milliliter. On the other hand, the majority of such patients in the triple drug therapy arm had indeed reached maximal suppression of viral replication. This becomes a critically important difference when the ultimate goal of the therapeutic strategy is to maximally suppress viral replication to prevent the emergence of resistance, as recently recommended.17-19

Also, recent data clearly demonstrate that only those patients who achieved high-level suppression of viral replication, as suggested by a nadir below 20 copies per milliliter, can sustain the antiretroviral response beyond 6 months.26

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