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 0.60×10^9/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<.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<.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=.08).

Conclusions.—Triple drug therapy with zidovudine, didanosine, and nevirapine led to an unexpectedly 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.

NEVIRAPINE, a potent and selective noncompetitive inhibitor of the reverse transcriptase enzyme of human immunodeficiency virus type 1 (HIV-1), belongs to the class of antiretroviral compounds referred to as nonnucleoside reverse transcriptase inhibitors. Nevirapine has a wide distribution throughout body tissues, including the central nervous system. Nevirapine has at least an additive in vitro antiviral effect with zidovudine, didanosine, and lamivudine, regardless of prior zidovudine exposure.

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. Consent was obtained from all patients aged 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 1.3 times the upper limit of the normal range; Karnofsky score below 80 points; use of immunosuppressive, cytotoxic, or experimental therapy within 4 weeks of entry; fever more than 38°C; weight loss more than 10% in the previous 6 months; and Larder15,16 at VIRCO Laboratories (Mechelen, Belgium). The threshold for decreased susceptibility (or resistance) 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 is 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 P 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 baseline except for plasma HIV-1 RNA, which was significantly lower in the triple drug therapy group. Ninety-nine (66%) of the 151 study patients completed the intended follow-up (Table 1).

Virologic Effect

As shown in Figure 1, all 3 groups showed a reduction in plasma HIV-1 RNA by week 4; however, substantial and persistent treatment-related differences developed thereafter. As early as week 8, plasma HIV-1 RNA decreased by approximately log 0.90, 1.56, and 2.18 in the zidovudine plus nevirapine, zidovudine plus didanosine, and triple drug therapy groups, respectively. Triple drug therapy reduced the plasma viral load to a significantly greater extent than zidovudine plus didanosine whether groups were compared using the nadir ($P = .001$), the area under the curve minus baseline ($P = .001$), or the decrease from baseline to the end-of-trial average ($P = .02$).

As shown in Figure 2, the proportion of patients who achieved high-level suppression of viral replication, as manifested by plasma HIV-1 RNA load levels below the limit of quantitation of the assay, was significantly greater in the triple drug therapy group ($P < .001$). 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, with 51% maintaining this level of suppression at week 52. This remained unchanged when a more stringent criterion was used; 45% (95% confidence interval, ±15%) of patients in the triple drug therapy group had HIV-1 RNA levels below 20 copies per milliliter at all visits between weeks 40 and 52. In contrast, only 6% (95% confidence interval, ±7%) and 0% of the patients treated with zidovudine plus didanosine and zidovudine plus nevirapine, respectively, had plasma HIV-1 RNA levels below 20 copies per milliliter at all visits between weeks 40 and 52. As shown in Table 3, the ranking of the study regimens remained the same whether the data were analyzed using a limit of quantitation of 20, 200, or 400 copies per milliliter.

Figure 3 shows the scatterplots of the change in plasma HIV-1 RNA load from baseline to the end-of-trial average against baseline plasma HIV-1 RNA load. For the zidovudine plus didanosine and triple drug regimens, noncompliance was frequently associated with failure to sustain maximal suppression of plasma HIV-1 RNA load. The rate of noncompliance was not significantly different among the 3 treatment groups ($P = .77$). In the triple drug therapy group, noncompliance occurred in 38 patients and was primarily associated with didanosine (55% [21/38], compared with...
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. No 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. Table 3 summarizes the plasma HIV-1 RNA levels below the limit of quantification from weeks 40 to 52.

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>&lt;400</td>
<td>0</td>
<td>8 (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>

*HIV-1 indicates human immunodeficiency virus type 1.
†Cochran-Mantel-Haenszel test, adjusting for country.
Figure 3.—Change in human immunodeficiency virus type 1 (HIV-1) RNA from baseline to weeks 40 through 52 vs baseline plasma RNA viral load for patients who complied for the full 52 weeks and those who did not comply for some part of the full 52 weeks in the zidovudine (ZDV) plus nevirapine (NVP) (A), ZDV plus didanosine (DDI) (B), and ZDV plus DDI plus NVP (C) groups. The diagonal dashed line represents the maximal virologic response ($y = \log (20 - x)$, determined using the Ultra Direct Assay).

Table 4.—Phenotypic Resistance to Study Medications at 6 Months in a Subset of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. With Virus Isolated</th>
<th>Zidovudine Resistance, No. (%)</th>
<th>Didanosine Resistance, No. (%)</th>
<th>Nevirapine Resistance, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine plus nevirapine</td>
<td>16</td>
<td>11</td>
<td>0</td>
<td>11 (69)</td>
<td></td>
</tr>
<tr>
<td>Zidovudine plus didanosine</td>
<td>19</td>
<td>9</td>
<td>4 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zidovudine plus didanosine plus nevirapine</td>
<td>24</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (21)</td>
</tr>
</tbody>
</table>

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 γ-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 didanosine group.
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 5 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 10 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 0.60 × 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 contrast, no change in plasma HIV-1 RNA levels was seen among patients who continued to receive zidovudine therapy. However, plasma HIV-1 RNA levels tended to return toward baseline after 12 weeks of therapy. More recently, results of the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group (ACTG) protocol 241 were reported by D’Aquila et al. A total of 398 patients with a CD4 cell count below 0.35 × 10^9/L who had previously received treatment with nucleoside analogues for more than 6 months were randomized to receive zidovudine plus didanosine with or without nevirapine. For the 198 subjects in the subset of this study with virologic analysis, the maximum decrease from baseline in plasma HIV-1 RNA load was 1.16 and 0.45 log copies per milliliter in the triple and double therapy arms, respectively. Again, these values tended to return toward baseline despite continued therapy.

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

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hairy leukoplakia</td>
<td>25/54 (47)</td>
</tr>
<tr>
<td>Oral candida</td>
<td>4/53 (7)</td>
</tr>
<tr>
<td>Herpes zoster virus infection</td>
<td>0/51 (2)</td>
</tr>
<tr>
<td>Oral hairy leukoplakia and herpes zoster virus infection</td>
<td>1/53 (2)</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>0/51 (2)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>0/51 (2)</td>
</tr>
<tr>
<td>Oral candida and herpes zoster virus infection</td>
<td>0/53 (1)</td>
</tr>
</tbody>
</table>

### 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>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Flattulence</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (66)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Abnormal liver function test results</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (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.
tient protease inhibitor or 2 nucleoside agents plus a nonnucleoside reverse transcriptase inhibitor. Direct comparative trials of these 2 treatment strategies have not been conducted. However, it is noteworthy that virologic responses similar to those seen in the INCAS Trial were recently reported within the AVANTI II study.27 This was a double-blind controlled study comparing zidovudine plus lamivudine plus either indinavir or an identical placebo among antiretroviral therapy–naïve patients with CD4 cell counts of 0.15 to 0.50 × 10^9/L. In the AVANTI II study, 60% of patients treated with zidovudine plus lamivudine plus indinavir had a plasma HIV-1 RNA level below 20 copies per milliliter at 52 weeks.28 Nearly identical results were recently reported when zidovudine plus lamivudine plus nevirapine was used in the AVANTI II study. Hence, at this time, the choice between 2 nucleoside agents plus a potent protease inhibitor or a nonnucleoside reverse transcriptase inhibitor cannot be made objectively based on the data available concerning antiretroviral efficacy. On the other hand, there are differences with regard to safety profile and dose scheduling between these regimens that may influence their selection in a particular clinical situation.

Until recently, resistance to nevirapine had been found to develop rapidly in vivo and in vitro.29 In vivo, this has been associated with rapid loss of the virologic effect. Although preliminary, the results of our phenotypic resistance studies conducted in a subset of patients strongly support the concept that high-level suppression of viral replication represents a valid strategy to prevent the development of nevirapine resistance and to prolong the therapeutic effect of this agent. In fact, it is expected that this strategy will be useful in enhancing and prolonging the therapeutic effect of currently available antiretroviral agents in general. The long-term impact of such a strategy is currently under investigation.

Our results highlight the important role of compliance. In fact, compliance becomes critically important in the context of therapeutic strategies intended to maintain a high level of suppression of viral replication as a way to prevent the emergence of resistance. Future efforts should be directed toward facilitating compliance by reducing the multiple constraints often associated with the increasing number of available antiretroviral regimens.29 Increased awareness of this issue in the appropriate patient counseling should lead to enhanced compliance. Of note, the former mint-flavored formulation of didanosine was used in our study. Compliance should improve with the use 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 the 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.4,25,27,28 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.3,14 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 antiviral response beyond 6 months.28,29

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