

# The New England Journal of Medicine

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VOLUME 339

OCTOBER 29, 1998

NUMBER 18



## MAINTENANCE ANTIRETROVIRAL THERAPIES IN HIV-INFECTED SUBJECTS WITH UNDETECTABLE PLASMA HIV RNA AFTER TRIPLE-DRUG THERAPY

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### ABSTRACT

**Background** Combination antiretroviral therapy with indinavir, zidovudine, and lamivudine can suppress the level of human immunodeficiency virus (HIV) RNA in plasma below the threshold of detection for two years or more. We investigated whether a less intensive maintenance regimen could sustain viral suppression after an initial response to combination therapy.

**Methods** HIV-infected subjects who had CD4 cell counts greater than 200 per cubic millimeter, who had been treated with indinavir, lamivudine, and zidovudine, and who had less than 200 copies of HIV RNA per milliliter of plasma after 16, 20, and 24 weeks of induction therapy were randomly assigned to receive either continued triple-drug therapy (106 subjects), indinavir alone (103 subjects), or a combination of zidovudine and lamivudine (107 subjects). The primary end point was loss of viral suppression, which was defined as a plasma level of at least 200 copies of HIV RNA per milliliter on two consecutive measurements during maintenance therapy.

**Results** During maintenance treatment, 23 percent of the subjects receiving indinavir and 23 percent of those receiving zidovudine and lamivudine, but only 4 percent of those receiving all three drugs, had loss of viral suppression ( $P < 0.001$  for the comparison between triple-drug therapy and the other two maintenance regimens). Subjects with greater increases in CD4 cell counts during induction therapy, higher viral loads at base line (i.e., at the beginning of induction therapy), and slower rates of viral clearance were at greater risk for loss of viral suppression. The presence of zidovudine-resistance mutations in HIV RNA at base line was strongly predictive of the loss of viral suppression in subjects treated with zidovudine and lamivudine.

**Conclusions** The suppression of plasma HIV RNA after six months of treatment with indinavir, zidovudine, and lamivudine is better sustained by the continuation of these three drugs than by maintenance therapy with either indinavir alone or zidovudine and lamivudine. (N Engl J Med 1998;339:1261-8.)

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COMBINATION antiretroviral regimens effectively reduce levels of human immunodeficiency virus (HIV) RNA in the plasma and lymph nodes, improve immune function, and delay the progression of HIV disease.<sup>1-5</sup> The recent recognition that a long-lived reservoir of HIV persists in latently infected CD4 cells, even among patients in whom HIV replication has been suppressed for two years, suggests the need for continued HIV therapy for many years, if not for life.<sup>6-8</sup> Regimens with multiple drugs are difficult for patients to adhere to and are associated with toxic effects and high cost. Simplified HIV-treatment strategies are needed.

The success of current antiretroviral therapy in maintaining viral suppression depends on the sustained inhibition of viral replication to the extent that levels are too low for drug-resistant mutants to emerge or viral rebound to occur. Because most HIV is generated within infected lymphocytes with a half-life of less than two days, the burden of HIV in the body rapidly diminishes after the initiation of potent antiretroviral therapy.<sup>9,10</sup> Levels of HIV in the plasma and lymph nodes, including levels of free virus associated with lymph-node follicular dendritic cells,<sup>2,3</sup> decline rapidly. We therefore reasoned that a less intensive antiretroviral regimen might maintain

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viral suppression in patients who had had a substantial reduction in infectious virus and infected cells in response to a potent antiretroviral regimen.

To test this treatment strategy, we administered a potent antiretroviral regimen to HIV-infected subjects for six months. The combination of indinavir, zidovudine, and lamivudine was chosen as the initial induction regimen because of its virologic potency and its tolerability.<sup>4,5</sup> Patients who had less than 200 copies of HIV RNA per milliliter of plasma during the induction period were then randomly assigned to receive continued three-drug therapy or one of two less intensive maintenance regimens, monotherapy with indinavir or combination therapy with zidovudine and lamivudine. The selection of these two regimens was based on the observation that each had successfully suppressed plasma HIV RNA for six months or more in the majority of patients with low but detectable levels of HIV.<sup>11,12</sup>

## METHODS

### Study Subjects

All study subjects were HIV-infected adults with a CD4 count of at least 200 cells per cubic millimeter and a plasma level of HIV RNA of at least 1000 copies per milliliter at study entry. Additional entry criteria included a Karnofsky performance-status score of at least 70 and the ability to provide written informed consent. Laboratory requirements were a hemoglobin level of at least 9.1 g per deciliter for men or 8.9 g per deciliter for women, a neutrophil count of at least 1000 per cubic millimeter, a platelet count of at least 65,000 per cubic millimeter, levels of hepatic aminotransferases no more than 5 times the upper limit of normal, serum bilirubin levels no more than 1.5 times the upper limit of normal, and serum creatinine levels no more than 2 times the upper limit of normal.

Subjects who had received HIV-protease-inhibitor therapy for more than two weeks or lamivudine or abacavir therapy at any time were not eligible. Other criteria for exclusion were known intolerance of zidovudine; moderate or severe peripheral neuropathy within 60 days before study entry; acute infection within 2 weeks before study entry; unexplained fever, chronic diarrhea, or hepatitis within 30 days before study entry; and cancer requiring systemic chemotherapy. Subjects could not have been treated with interferon, granulocyte-macrophage colony-stimulating factor (GM-CSF), or HIV vaccines within 30 days before study entry, rifampin or rifabutin within 2 weeks before study entry, or drugs contraindicated in the presence of indinavir. All women of childbearing potential had a pregnancy test at entry, and pregnant women were excluded. All enrollees gave written informed consent.

### Study Design

This was a double-blind, randomized study comparing the antiretroviral activity of three maintenance regimens in patients in whom plasma HIV RNA levels were first suppressed by a six-month course of triple-drug induction therapy. The study was conducted with the approval of the institutional review boards of all 39 participating institutions.

In the first part of the study, the induction phase, the subjects received open-label treatment with indinavir (Crixivan, Merck, West Point, Pa.; 800 mg every eight hours), lamivudine (EpiVir, Glaxo Wellcome, Research Triangle Park, N.C.; 150 mg twice daily), and zidovudine (Retrovir, Glaxo Wellcome; 300 mg twice daily) for 24 weeks. Pretreatment evaluations included a clinical assessment, collection of two plasma samples for measurement of baseline HIV RNA levels, two assessments of T-lymphocyte subtypes,

and collection of a plasma sample later analyzed for viral mutations conferring resistance to zidovudine and lamivudine by the line-probe reverse-transcriptase assay.<sup>13</sup> For subjects who had adverse reactions to zidovudine during the study, a reduction in the dose to 100 mg three times daily was allowed. Zidovudine-intolerant subjects were permitted to substitute stavudine (Zerit, Bristol-Myers Squibb, Princeton, N.J.) for zidovudine. Subjects who could not tolerate full-dose stavudine, lamivudine, or indinavir were withdrawn from the trial. Assessment of drug toxicity, routine laboratory monitoring, and determination of T-lymphocyte subtypes by flow cytometry were performed at intervals of four to eight weeks throughout the study. Plasma for HIV RNA determination was obtained every 4 weeks, stored at  $-70^{\circ}\text{C}$ , and assayed at a central laboratory after 24 weeks of induction therapy.

In the second part of the study, the maintenance phase, subjects were randomly assigned to receive one of three regimens in a double-blind fashion. The regimens were indinavir monotherapy, zidovudine (or stavudine) and lamivudine, and the original triple-drug combination, given at the previously mentioned doses. Random assignment to one of the three maintenance treatments proceeded only for subjects who had HIV RNA levels of less than 200 copies per milliliter at weeks 16, 20, and 24. Randomization was performed centrally, with stratification according to the baseline number of copies of HIV RNA per milliliter of plasma (30,000 or more vs. less than 30,000) and the number of days of zidovudine therapy before the study began (seven days or more vs. fewer than seven days). Induction therapy was considered to have failed in subjects who had less than 200 copies of HIV RNA per milliliter of plasma at weeks 16, 20, and 24 but who had 200 or more copies per milliliter on the day of random assignment to maintenance therapy.

During maintenance therapy, levels of HIV RNA were monitored weekly for four weeks, at week 8, and then every eight weeks thereafter. Subjects who had a confirmed loss of suppression of plasma HIV RNA, indicated by an increase to 200 or more copies per milliliter, were allowed to receive open-label triple-drug therapy or to seek alternative therapy.

### End Point

The primary end point of the study was loss of viral suppression during maintenance therapy, defined as an increase in the level of HIV RNA to at least 200 copies per milliliter of plasma, confirmed in a second specimen. Levels of HIV RNA were determined at the Johns Hopkins Medical Laboratory with the ultra-sensitive version of the Roche Amplicor HIV Assay (Roche Molecular Systems, Alameda, Calif.).

### Monitoring

Subjects were randomly assigned to receive one of three maintenance-therapy regimens beginning in August 1997; an interim review was triggered in November 1997. The first review included 37 end points accumulated as of December 19, 1997, and was performed on January 5, 1998. The results of this review showed significant differences in suppression of HIV RNA among the three maintenance therapies, which met the prespecified guidelines for stopping the study.<sup>14</sup> The study was therefore terminated in its original form on January 5, 1998.

### Statistical Analysis

Only data pertaining to evaluations on or before the date of the interim review (January 5, 1998) were analyzed. All analyses were performed according to the intention-to-treat approach. Univariate analyses were performed with use of Fisher's exact test for pairwise comparisons of the proportions of subjects with sustained viral suppression in the three treatment groups. Plots of the estimated proportion of subjects with sustained viral suppression over time were constructed by the Kaplan-Meier method and were compared with use of the log-rank test.<sup>15</sup> The results of the Fisher's exact test and the log-rank test were highly consistent with each other.

Multivariate analyses were based on the Cox proportional-hazards model for the length of time to loss of viral suppression.<sup>15</sup> The following predictors of time to loss of viral suppression were evaluated in stepwise regression analyses: zidovudine therapy received before induction therapy (six months or less vs. more than six months); presence or absence of genotypic zidovudine resistance at base line (i.e., before induction therapy); HIV RNA level at base line; time until viral suppression was achieved during induction therapy; whether or not the plasma HIV RNA level was below 50 copies per milliliter at weeks 16, 20, and 24; CD4 cell count at base line; and increase in the CD4 cell count during induction therapy. In addition, the significance of interactions among these predictors and the treatment group was tested to assess whether the effect of predictors depended on the treatment group. In these multivariate analyses, zidovudine resistance was defined as a mutation at codon 215, or at codon 41 if the genotype for codon 215 was unavailable for technical reasons.

Multivariate analyses were repeated with use of logistic regression to model the proportion of subjects with sustained viral suppression, after adjustment for the length of follow-up. The results of these analyses were consistent with the results of the Cox model and are therefore not presented here. Levels of HIV RNA were analyzed after logarithmic transformation (to a log<sub>10</sub> scale), whereas untransformed CD4 counts were analyzed. Base-line HIV RNA levels and CD4 counts were determined by averaging the values measured at and before the beginning of induction therapy. All reported P values are two-sided.

**RESULTS**

**Accrual and Study Population**

A total of 509 subjects were enrolled in the study between February 20 and April 30, 1997. During

the induction phase, 30 subjects prematurely discontinued treatment because of symptoms attributed to the study medications, and 37 voluntarily withdrew from the study for other reasons. HIV RNA measurements were available for 420 subjects at weeks 16, 20, and 24. Of these, 345 subjects had HIV RNA levels of less than 200 copies per milliliter of plasma at all three times.

Twenty-nine of the 345 subjects qualified for randomization to maintenance therapy but voluntarily withdrew from the study before randomization, and 316 consented to be randomly assigned to treatment in the maintenance phase. Seven of these 316 subjects were later found to have had an HIV RNA measurement of 200 or more copies per milliliter of plasma after week 24, but before maintenance therapy was started. In these cases, induction therapy was considered to have failed, and they were omitted from all subsequent analyses, leaving a total of 309 subjects in the study sample.

At base line, the subjects randomly assigned to maintenance therapy had a median CD4 cell count of 448 cells per cubic millimeter and a median plasma HIV RNA level of 11,813 copies per milliliter. Forty-three percent of the study subjects had been previously treated with zidovudine for 7 days or longer, with a median duration of treatment of 90 weeks. Base-line characteristics were similar among the study

**TABLE 1. BASE-LINE CHARACTERISTICS OF SUBJECTS RANDOMLY ASSIGNED TO MAINTENANCE THERAPY.\***

CHARACTERISTIC	ALL PATIENTS (N=316)	INDINAVIR (N=103)	ZIDOVUDINE AND LAMIVUDINE (N=107)	INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE (N=106)
Male sex (%)	86	86	87	86
Race or ethnic group (%)				
White	67	66	68	66
Black	21	19	20	23
Hispanic	10	12	11	8
Other	3	3	1	4
Median age (yr)	37	35	37	37
Prior zidovudine therapy ≥7 days (%)	43	42	45	42
CD4 count (cells/mm <sup>3</sup> )				
Median	448	477	447	442
Range	153–1540	209–1208	153–1540	187–1005
Plasma HIV RNA (log <sub>10</sub> copies/ml)				
Median	4.1	4.1	4.1	4.0
Range	1.3–5.9	2.6–5.7	1.3–5.4	2.0–5.9
Codon with zidovudine-resistance mutation (%)†				
215	14	10	17	15
70	20	18	16	25
41	12	7	19	11

\*Base-line characteristics are those measured at the beginning of induction therapy. Some subjects who had adverse effects of zidovudine therapy received stavudine instead. Data were not available for all subjects in some cases.

†Percentages are of the total number of subjects in the group. Some subjects had more than one mutation.

groups (Table 1). The overall study population of 509 subjects and the population randomly assigned to maintenance therapy (316 subjects) had similar base-line characteristics (data not shown).

**Study Treatment and Follow-up**

In the study population randomly assigned to treatment groups, viral suppression was achieved during induction therapy in 56 percent, 81 percent, and 93 percent of subjects at 4, 8, and 12 weeks, respectively. The overall mean increase in the CD4 cell count from base line to random assignment to maintenance therapy was 143 cells per cubic millimeter. The mean CD4 cell count was 618 per cubic millimeter at the time of randomization. The median follow-up during the maintenance phase was 8 weeks (range, 0.1 to 16).

Of the 309 subjects in the final study sample, 42 had intolerance of zidovudine, 6 of whom continued therapy at a reduced dose (100 mg of zidovudine three times daily). Thirty-six subjects switched to stavudine. Among the subjects receiving zidovudine, neutropenia was reported in 27, nausea in 26, fatigue in 20, headache in 9, and anemia in 6. Nephrolithiasis developed in 19 subjects receiving indinavir.

**Study End Points**

Loss of HIV RNA suppression occurred during the maintenance phase but before termination of the study in 51 subjects (17 percent): 23 subjects (23 percent) receiving indinavir, 24 subjects (23 percent) receiving zidovudine (or stavudine) plus lamivudine, and 4 subjects (4 percent) receiving triple-drug therapy (Table 2). The proportion of subjects with loss of viral suppression in the triple-drug group was significantly lower than that in either of the two experimental groups ( $P < 0.001$  in each case). The time to the return of detectable HIV RNA in the plasma was significantly shorter in the indinavir group and the zidovudine-lamivudine group than in the triple-drug group ( $P < 0.001$  for each comparison) (Fig. 1).

In the zidovudine-lamivudine group, the proportion with end points was much higher among subjects with more than six months of previous zidovudine therapy than among subjects with six months or less of zidovudine therapy (45 percent vs. 11 percent,  $P < 0.001$ ) (Table 2). The difference between the proportion of subjects with loss of viral suppression in the zidovudine-lamivudine group and that in the triple-drug group was large among subjects with more than six months of zidovudine treatment (45 percent vs. 3 percent,  $P < 0.001$ ), and smaller among subjects with six months or less of zidovudine treatment (11 percent vs. 4 percent,  $P = 0.20$ ). The presence of zidovudine-resistance mutations at base line was highly associated with the loss of viral suppression in the zidovudine-lamivudine group. In 10 of 14 subjects in this group (71 percent) with base-

**TABLE 2.** PROPORTION OF SUBJECTS WITH LOSS OF VIRAL SUPPRESSION DURING MAINTENANCE THERAPY, ACCORDING TO TREATMENT GROUP.

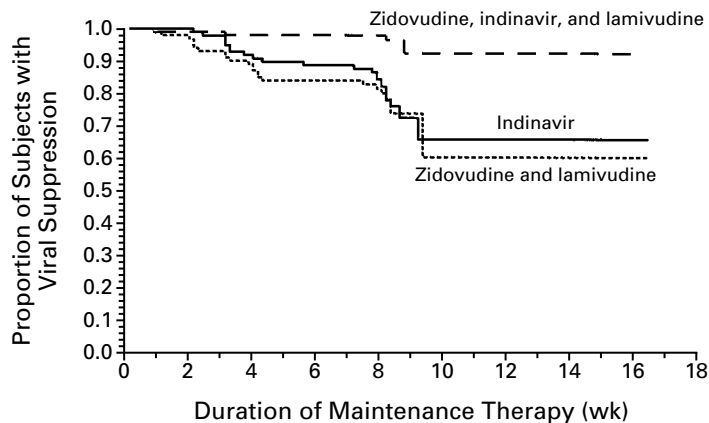
CHARACTERISTIC*	INDINAVIR (N=100)	ZIDOVUDINE AND LAMIVUDINE (N=104)†	INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE (N=105)‡
	no./total no. (%)		
All subjects (n=309)	23 (23)	24 (23)	4 (4)
Prior zidovudine therapy			
≤6 mo (n=205)	15/69 (22)	7/66 (11)	3/70 (4)
>6 mo (n=104)	8/31 (26)	17/38 (45)	1/35 (3)
Codon with zidovudine-resistance mutation at base line‡			
215			
Wild type (n=211)	14/73 (19)	10/67 (15)	3/71 (4)
Mutant (n=35)	3/8 (38)	10/14 (71)	0/13
70			
Wild type (n=194)	15/63 (24)	13/66 (20)	4/65 (6)
Mutant (n=49)	3/14 (21)	7/13 (54)	0/22
41			
Wild type (n=219)	17/77 (22)	10/64 (16)	4/78 (5)
Mutant (n=31)	2/6 (33)	9/15 (60)	0/10
Base-line plasma HIV RNA (copies/ml)			
<5000 (n=95)	5/27 (19)	3/29 (10)	0/39
5000–30,000 (n=129)	7/44 (16)	12/49 (24)	1/36 (3)
>30,000 (n=84)	10/28 (36)	9/26 (35)	3/30 (10)
First week of induction therapy with HIV RNA <200 copies/ml			
4 (n=174)	9/61 (15)	7/54 (13)	0/59
8 (n=76)	7/20 (35)	10/29 (34)	2/27 (7)
12 or 16 (n=59)	7/19 (37)	7/21 (33)	2/19 (11)
Base-line CD4 count (cells/mm <sup>3</sup> )			
<350 (n=88)	5/25 (20)	6/28 (21)	1/35 (3)
350–500 (n=101)	8/32 (25)	13/38 (34)	2/31 (6)
>500 (n=120)	10/43 (23)	5/38 (13)	1/30 (3)
Increase in CD4 count during induction therapy (cells/mm <sup>3</sup> )			
<50 (n=78)	4/27 (15)	0/24	0/27
50–150 (n=88)	8/26 (31)	5/32 (16)	1/30 (3)
>150 (n=143)	11/47 (23)	19/48 (40)	3/48 (6)

\*The numbers of subjects with each characteristic are shown in parentheses. Data were not available for all subjects in some cases. Base-line characteristics are those measured at the beginning of induction therapy.

†Some subjects who had adverse effects of zidovudine received stavudine instead.

‡Some subjects had more than one mutation.

line isolates exhibiting a mutation in codon 215 of the gene for reverse transcriptase, detectable levels of HIV RNA developed, as compared with none of the 13 subjects in the triple-drug group who had this mutation ( $P < 0.001$ ). Among subjects without a base-line mutation in codon 215, detectable levels of HIV RNA developed in 10 of 67 subjects (15 percent) in the zidovudine-lamivudine group, as compared with 3 of 71 subjects (4 percent) in the triple-drug group ( $P = 0.041$ ). In contrast, the development of detectable levels of HIV RNA in subjects in the indinavir



NO. AT RISK	0	2	4	6	8	10	12	14	16	18
Zidovudine, indinavir, and lamivudine	105	101	98	94	44	6	3	2	0	
Zidovudine and lamivudine	104	96	83	78	34	5	3	3	1	
Indinavir	100	99	88	85	39	6	4	3	1	

**Figure 1.** Kaplan–Meier Estimates of the Proportion of Subjects in Whom the Primary Study End Point of Loss of Viral Suppression Was Not Reached during Maintenance Therapy.

P<0.001 for the comparison between triple-drug therapy and each of the other treatments. Some subjects who had adverse effects of zidovudine received stavudine instead.

group was not significantly associated with prior zidovudine therapy or base-line zidovudine-resistance mutations (Table 2).

The rate of loss of viral suppression was higher among subjects with higher levels of HIV RNA at the beginning of induction therapy (base-line levels). Among those with more than 30,000 copies of HIV RNA per milliliter of plasma at study entry, 26 percent had a return of detectable plasma HIV RNA, as compared with 8 percent of those with no more than 5000 copies per milliliter of plasma. The mean base-line number of copies of HIV RNA per milliliter of plasma was 20,893 in subjects with loss of viral suppression during maintenance therapy and 9057 in those with sustained suppression (P<0.001). Subjects in whom viral suppression occurred by week 4 of induction therapy had a much lower failure rate (9 percent) than those in whom viral suppression occurred later (26 percent, P=0.0015). The rate of loss of viral suppression was 15 percent among subjects with less than 50 copies of HIV RNA per milliliter of plasma at weeks 16, 20, and 24, as compared with 21 percent in those with 50 to 200 copies per milliliter of plasma during this interval (P=0.21).

The magnitude of the change in the CD4 cell count during induction therapy was highly correlated with the proportion of subjects in whom viral suppression was lost during maintenance therapy. Viral suppression was lost in 23 percent of subjects who had an increase in the CD4 count of more than 150

cells per cubic millimeter and in only 5 percent of subjects who had an increase of less than 50 cells per cubic millimeter. The mean increase in CD4 cell count among subjects with loss of viral suppression during maintenance therapy was 210 per cubic millimeter, as compared with 130 per cubic millimeter among those in whom viral suppression was sustained (P<0.001). CD4 cell counts at base line and before randomization to maintenance therapy did not differ significantly between those in whom viral suppression was sustained and those in whom it was lost (P=0.21 at base line, and P=0.28 before randomization). Furthermore, the proportion of subjects in whom viral suppression was lost did not vary according to the base-line CD4 count or the CD4 count before randomization (Table 2).

**Multivariate Modeling of Loss of Viral Suppression**

In the multivariate analysis (Table 3), the presence of genotypic zidovudine resistance was a significant predictor of loss of viral suppression in the zidovudine–lamivudine group but not in the other two groups (test for interaction, P<0.001). Among subjects with zidovudine-resistance mutations (that is, mutations at codon 215, or codon 41 if the genotype at codon 215 was unavailable), the rate of loss of viral suppression during the maintenance phase was 27.2 times as high (95 percent confidence interval, 9.4 to 88.0) among those receiving zidovudine plus lamivudine as among those receiving triple-drug therapy.

**TABLE 3.** MULTIVARIATE RELATIVE RISK OF LOSS OF VIRAL SUPPRESSION DURING MAINTENANCE THERAPY.

VARIABLE*	RELATIVE RISK (95% CI)†	P VALUE
Indinavir (vs. triple-drug therapy)	5.8 (2.0–16.8)	0.0013
Zidovudine (or stavudine) and lamivudine (vs. triple-drug therapy)		
Zidovudine-sensitive virus	3.0 (0.94–9.7)	0.063
Zidovudine-resistant virus‡	27.2 (9.4–88.0)	<0.001
Plasma HIV RNA >200 copies/ml at week 4	2.5 (1.3–4.7)	0.004
CD4 cell increase	1.3 (1.1–1.6)§	0.0015

\*All other variables listed in the Methods section were not associated with an increased risk of the loss of viral suppression ( $P > 0.10$ ).

†CI denotes confidence interval.

‡A zidovudine-resistant virus was defined as one with a mutation at codon 215, or with a mutation at codon 41 if information on codon 215 was unavailable.

§The relative risk is expressed as the risk associated with an increase of 100 CD4 cells per cubic millimeter during induction therapy.

Subjects without base-line resistance who were receiving zidovudine plus lamivudine had a marginally significant ( $P = 0.063$ ) but smaller increase (by a factor of 3.0; 95 percent confidence interval, 0.94 to 9.7) in the rate of loss of viral suppression than those receiving triple-drug therapy. Mutations at codons 41, 70, or 41 and 215 did not independently predict the loss of viral suppression after adjustment for genotypic zidovudine resistance, as defined above.

A longer duration of prior zidovudine treatment was highly associated with zidovudine resistance but was not an independent predictor of the loss of viral suppression in the multivariate analysis. Ninety-three percent of subjects with base-line genotypic zidovudine resistance had had at least six months of prior zidovudine therapy. Thus, in this population, treatment history accurately predicted the presence or absence of a mutation at codon 215.

A longer time to viral suppression during the induction phase was an independent predictor of the loss of viral suppression. Subjects with HIV RNA levels greater than or equal to 200 copies per milliliter at week 4 of induction therapy had a risk of loss of viral suppression that was 2.5 times as high (95 percent confidence interval, 1.3 to 4.7) as that among subjects with lower levels at week 4. Base-line levels of HIV RNA were not independently predictive after adjustment for the time to viral suppression because of the strong association between these two variables. As in the univariate analysis, loss of viral suppression was predicted by a greater increase from base line in the CD4 cell count at week 28, but not by the base-line value or the value at week 28. Every increase of 100 in the CD4 cell count was associated with a relative risk of 1.3 (95 percent confidence interval, 1.1 to 1.6) for the loss of viral suppression.

The use of stavudine in place of zidovudine was not an independent predictor of viral suppression in the multivariate analysis.

## DISCUSSION

Potent combination antiretroviral therapy has dramatically reduced the rates of opportunistic infection, hospitalization, and mortality among HIV-infected patients and thus has offered the hope that HIV infection can be successfully managed as a chronic disease.<sup>16,17</sup> These benefits remain limited to those who can tolerate, adhere to, and afford complex therapies for prolonged periods. We hypothesized that a potent antiretroviral regimen would reduce the HIV burden in the body to a level that would permit the use of a less intensive, less toxic, and less expensive regimen to maintain viral suppression. We found, however, that after six months, the degree of viral suppression achieved with an induction regimen of indinavir, zidovudine (or stavudine), and lamivudine was not sustained by a maintenance regimen consisting of either indinavir monotherapy or zidovudine (or stavudine) plus lamivudine. Partial withdrawal of drug therapy led to prompt viral rebound in 23 percent of subjects.

The failure of maintenance therapy may be attributed to inadequate inhibition of viral replication from productively infected cells. Although the levels of HIV RNA were reduced to below 50 copies per milliliter of plasma in 98 percent of subjects, the remaining pool of infected cells must still have been of sufficient size after six months of therapy to preclude effective suppression with a simpler, less potent antiviral regimen. Furthermore, increased lymphocyte proliferation may have increased the number of cells susceptible to HIV infection and thus permitted propagation of virus in the presence of diminished efficacy of the antiviral drugs.<sup>18,19</sup> As predicted by mathematical simulations incorporating target-cell availability, subjects with the greatest increases in CD4 cell counts were at highest risk for the return of detectable HIV RNA in the plasma during the maintenance phase.<sup>20</sup>

As have previous investigators, we found that higher levels of plasma HIV RNA at the onset of treatment and longer periods of detectable virus before clearance predicted less sustained viral suppression.<sup>5,21</sup> The base-line viral loads were nearly three times as high in subjects in whom plasma HIV RNA became detectable during maintenance therapy as in those in whom it did not. Prompt viral suppression may identify subjects who have the greatest reduction in viral burden and for whom maintenance regimens will be the most effective in sustaining viral suppression. Alternatively, rapid viral suppression may reflect greater adherence to the regimen by the subject.

Prior zidovudine therapy and the presence of zidovudine-resistance mutations at base line were highly

predictive of the loss of viral suppression in subjects receiving the maintenance regimen of zidovudine (or stavudine) and lamivudine. The potency and durability of viral suppression produced by a zidovudine-lamivudine combination are known to be diminished in patients with prior zidovudine therapy.<sup>22,23</sup> The combination of zidovudine and lamivudine may also be inadequate maintenance therapy in patients not previously treated with zidovudine. In this subgroup, the percentage of therapeutic failures in our subjects receiving zidovudine (or stavudine) and lamivudine (11 percent) was greater than that in subjects receiving triple-drug therapy (4 percent), although this difference was not statistically significant.

The results of this trial provide several important practical insights into the limitations of currently recommended combination antiretroviral therapy. First, the efficacy of suppressive regimens leaves little margin for error. Poor adherence to even one component of a regimen may result in the loss of viral suppression. Second, preexisting drug-resistance mutations may compromise the efficacy of a regimen and put patients at high risk for the return of detectable levels of HIV RNA in the plasma even after viral suppression has been achieved. Finally, elevations of CD4 cell counts may paradoxically increase the risk of the loss of viral suppression by generating more host cells in which virus can replicate.

Although the results of this trial are somewhat disappointing, they should not discourage future attempts to simplify therapies for HIV. Data from this trial and from two other recently completed trials of induction and maintenance therapy in patients without prior antiretroviral treatment argue that induction therapy, maintenance therapy, or both must have greater virologic potency than the regimens used in these trials if they are to sustain viral suppression.<sup>24,25</sup> Simplification of therapy may be possible without sacrificing potency if some of the highly active drugs in development, which require only once-daily dosage, become available.<sup>26-28</sup> It is also possible, as suggested by studies in vitro, that longer induction periods may result in better success when patients are switched to simplified maintenance regimens.<sup>29</sup>

The results of this trial also provide a rationale for new immunologic approaches to HIV therapy. Limiting the activation and available pool of target cells in patients during sustained HIV suppression may be beneficial and may reduce the risk of viral rebound.<sup>18,30</sup> Promising results have been observed in studies of hydroxyurea, a drug known to inhibit cellular activation, and additional candidates are undergoing evaluation.<sup>31,32</sup>

Supported by grants from the AIDS Clinical Trials Group, Center for AIDS Research, National Institute of Allergy and Infectious Diseases (AI27670, AI38858, and AI36214), the National Institutes of Health (AI29164), and the Research Center for AIDS and HIV Infection of the San Diego Veterans

Affairs Medical Center. The study medications were provided by Merck, Glaxo Wellcome, and Bristol-Myers Squibb.

*We are indebted to all the participants in the trial; to Daniel Kuritzkes for comments on the manuscript; to Henry Chang for his support in the conduct of the trial; to John Svinisky and Roche Molecular Systems for providing HIV RNA assay kits; to Brooks Jackson and his staff at Johns Hopkins Medical Laboratories for performing the HIV RNA assays; to the National Genetics Institute, Culver City, California, and Murex Diagnostics, Norcross, Georgia, for performing genotypic assays for zidovudine and lamivudine resistance; and to Samantha Maddox and Judy Highfill for technical assistance.*

## APPENDIX

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