

A RANDOMIZED TRIAL OF THREE MAINTENANCE REGIMENS GIVEN AFTER THREE MONTHS OF INDUCTION THERAPY WITH ZIDOVUDINE, LAMIVUDINE, AND INDINAVIR IN PREVIOUSLY UNTREATED HIV-1-INFECTED PATIENTS

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ABSTRACT

Background The long-term effectiveness of potent three-drug antiretroviral regimens for the treatment of human immunodeficiency virus type 1 (HIV-1) infection is limited by problems related to compliance and tolerability. We investigated whether two-drug maintenance therapy would suppress viral replication after a three-month period of aggressive triple-drug induction therapy.

Methods A total of 378 HIV-1-infected adults who had not received previous antiretroviral treatment received three months of induction therapy consisting of 300 mg of zidovudine every 12 hours, 150 mg of lamivudine every 12 hours, and 800 mg of indinavir every 8 hours. The 279 patients in whom the plasma HIV-1 RNA titer fell below 500 copies per milliliter after two months of triple-drug therapy, and who completed the induction phase, were randomly assigned at month 3 to one of the following three open-label maintenance regimens: zidovudine, lamivudine, and indinavir; zidovudine and lamivudine; or zidovudine and indinavir. The primary end point was an increase in HIV-1 RNA levels to 500 copies or more per milliliter during the maintenance phase.

Results The proportion of patients who reached the primary end point was significantly higher among patients receiving zidovudine plus lamivudine (29 of 93 patients, $P < 0.001$) or zidovudine plus indinavir (21 of 94, $P = 0.01$) than among patients receiving continued triple-drug therapy (8 of 92). This higher failure rate in the groups treated with the two-drug maintenance regimens was also observed in the subgroup of patients with maximally suppressed HIV-1 RNA (below 50 copies per milliliter) at the time of randomization to maintenance therapy.

Conclusions In HIV-1-infected adults not previously treated with antiretroviral drugs whose plasma HIV-1 RNA levels fell below 500 copies per milliliter after three months of induction therapy with zidovudine, lamivudine, and indinavir, two-drug maintenance therapy was less effective in sustaining a reduced viral load than continued three-drug therapy. (N Engl J Med 1998;339:1269-76.)

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TREATMENT of human immunodeficiency virus type 1 (HIV-1) infection with two nucleoside analogues plus a protease inhibitor is aimed at reducing plasma viral titers and keeping them below the detection limit and represents the current standard of antiretroviral therapy.¹⁻³ The combination of zidovudine, lamivudine, and indinavir reduces plasma HIV-1 RNA levels to below 500 copies per milliliter for up to two years in more than 80 percent of HIV-1-infected patients.^{4,5} It is hoped that this sustained reduction in plasma HIV-1 RNA levels will translate into immune reconstitution, delayed progression to the acquired immunodeficiency syndrome (AIDS), and longer survival.⁶⁻¹³

The dynamics of populations of HIV-1-infected cells in treated patients suggest that treatment will have to be maintained for many years.¹⁴⁻¹⁶ However, the long-term effectiveness of regimens including a protease inhibitor is strongly dependent on strict daily compliance with treatment.^{17,18} Because of the constraints and potential side effects of triple-drug therapy including a protease inhibitor, alternative strategies are being sought to suppress viral replication without allowing the emergence of resistant mutants.^{19,20} We initiated the Trilège (Agence Nationale de Recherches sur le SIDA 072) trial to investigate whether the antiviral effect of a three-month induction regimen consisting of zidovudine (Retrovir, Glaxo Wellcome, Paris), lamivudine (Epiriv, Glaxo Wellcome), and indinavir (Crixivan, Merck Sharp and Dohme Chibret, Paris) could be maintained by a two-drug maintenance regimen.

METHODS

Study Design and Patients

During the induction phase, all the participants initially received 300 mg of zidovudine every 12 hours, 150 mg of lamivudine every 12 hours, and 800 mg of indinavir every 8 hours for three

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months. The time of enrollment in the induction phase was defined as the base line.

At the end of the induction phase, participants who had not had severe adverse reactions to any of the three drugs, and who had an HIV-1 RNA titer below 500 copies per milliliter of plasma at month 2, were randomly assigned (in a 1:1:1 ratio) to one of the following three maintenance regimens: zidovudine, lamivudine, and indinavir; zidovudine and lamivudine; or zidovudine and indinavir. In all the maintenance regimens, the drugs were administered at the same daily doses and on the same schedule as in the induction phase. The randomization was stratified according to base-line HIV-1 RNA level (below 30,000 copies per milliliter or 30,000 copies or more), but the trial did not have sufficient power to determine the most effective therapy for these two groups of patients separately. We planned to enroll 350 patients in the induction phase in order to have 100 subjects randomly assigned to each of the three maintenance regimens. Follow-up was planned to last 15 months after randomization.

The inclusion criteria were an age of 18 years or older, a CD4 cell count of less than 600 per cubic millimeter, a Karnofsky score of at least 70, no previous antiretroviral therapy, and base-line plasma levels of HIV-1 RNA between 3500 and 100,000 copies per milliliter (Amplicor assay, Roche, Paris). Patients were recruited at 43 AIDS clinical-trial units in France. The study was approved by the institutional review boards of the participating institutions, and all patients gave their written informed consent. Prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis was permitted; the use of full-dose rifabutin was prohibited. Data on compliance were collected and reported by the site investigators and were analyzed to produce the rate of adherence to the study regimens.

Study End Points

The primary end point was the time to virologic failure, defined as the first plasma HIV-1 RNA value of 500 copies per milliliter or more, confirmed in a second specimen six weeks later. The safety assessment was based on the number of clinical and biologic adverse events graded 3 or 4 (according to the AIDS Clinical Trials Group grading system) and those requiring discontinuation of treatment. The secondary end point was the change in the CD4 cell count during the maintenance phase.

Monitoring and Enrollment

Patients were assessed at enrollment and at weeks 2, 4, 8, and 12 during the induction phase. During the maintenance phase, clinical and biologic assessments were carried out every six weeks from the time of randomization (week 12) until the end of the study (week 72). CD4 cell counts and plasma HIV-1 RNA levels were measured every 12 weeks.

Plasma HIV-1 RNA levels were assessed in each participating center with the Amplicor HIV-1 assay (limit of detection, 200 copies per milliliter). A quality-control procedure was set up before the trial to assess the accuracy and reproducibility of the assay at the cutoff point of 500 copies per milliliter in the 29 laboratories. HIV-1 RNA levels above 500 copies per milliliter triggered backward testing of the plasma sample collected and stored six weeks previously. If the value was more than 500 copies per milliliter, virologic failure was considered to have occurred. If the value was less than the cutoff value, real-time forward examination of the specimen collected six weeks later was performed. Each virologic end point was validated by the study virologist, who reviewed the raw optical-density values of the run. Plasma HIV-1 RNA was also quantified at month 3 in selected laboratories with use of the ultrasensitive Roche assay (detection limit, 50 copies per milliliter).

Patients who discontinued the study medications or withdrew from the protocol for any reason (because of side effects, for personal reasons, or because they reached a study end point) were followed up for adverse events, clinical outcome, and biologic changes.

The first interim analysis of efficacy and safety by the independent data and safety monitoring board was planned for February

1998, the midpoint of follow-up during the maintenance period (a total of 2500 patient-months). In October 1997, the number of virologic failures was higher than expected, leading to an interim analysis in December 1997. On December 19, 1997, the data and safety monitoring board reviewed the data and recommended that the trial be terminated, following the stopping rule specified in the protocol with a spending function of $P=0.01$. The decision was endorsed by the scientific committee.

Statistical Analysis

The times to virologic failure were compared among the treatment groups by means of Kaplan–Meier estimates and log-rank tests. Stratified and unstratified analyses were carried out according to the plasma level of HIV-1 RNA at base line or at randomization. Fisher's exact test was used to compare the proportions of subjects in the three groups whose HIV-1 RNA levels remained below 500 copies per milliliter during the maintenance phase. The proportional-hazards model was used to identify links among the risk of virologic failure and base-line characteristics, early changes (from base line to randomization), and HIV-1 RNA levels and CD4 cell counts at randomization. Changes in CD4 cell counts with time in the three groups were compared with use of the Wilcoxon rank-sum test. Proportions of adverse events per treatment group were compared with use of Fisher's exact test. Follow-up data were censored at the time virologic failure occurred (the primary end point) and were restricted to patients randomly assigned to a maintenance treatment after three months of induction therapy who had actually received the induction treatment. All analyses of data from the maintenance period were conducted on an intention-to-treat basis, with two-sided tests of hypotheses at the 0.05 significance level.

RESULTS

Characteristics at Base Line and at Randomization

From November 1996 to October 1997, 378 patients were enrolled in the induction phase of the study. Of these, 362 completed three months of induction therapy, and 312 were eligible for randomization to maintenance treatment, with plasma levels of HIV-1 RNA below 500 copies per milliliter. Thirty-three of these patients (11 percent) did not enter the maintenance phase because of adverse events or a personal decision. Thus, 279 patients were finally randomly assigned to one of the three maintenance treatments: 92 to the triple-drug regimen, 93 to zidovudine plus lamivudine, and 94 to zidovudine plus indinavir. The characteristics of the enrolled and randomized subjects were similar (Table 1). In the population randomly assigned to maintenance therapy, the mean base-line level of HIV-1 RNA was 40,713 copies per milliliter (\log_{10} [\pm SD], 4.5 ± 0.3) and the median CD4 cell count was 363 per cubic millimeter (interquartile range, 280 to 440). Two hundred twenty patients (79 percent) had had no AIDS-defining events at enrollment. The base-line characteristics of the patients randomly assigned to maintenance therapy were well balanced among the three treatment groups (data not shown).

Levels of HIV-1 RNA measured with the ultrasensitive assay were available at month 3 for 265 of the 279 patients who began maintenance therapy; 191 (72 percent) had less than 50 copies of HIV-1 RNA per milliliter. HIV-1 RNA values below 50 copies per

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE AND AT RANDOMIZATION TO MAINTENANCE THERAPY.*

CHARACTERISTIC	AT BASE LINE (N=378)	AT RANDOMIZATION (N=279)
Sex — no. (%)		
Male	280 (74)	214 (77)
Female	98 (26)	65 (23)
Median age — yr	36.0±9	36.0±9
HIV risk factor — no. (%)		
Homosexual or bisexual activity	196 (52)	148 (53)
Heterosexual activity	127 (34)	94 (34)
Intravenous drug use	40 (11)	23 (8)
Transfusion or hemophilia	5 (1)	4 (1)
Undetermined	14 (4)	12 (4)
CDC disease stage — no. (%)		
A	297 (79)	220 (79)
B	68 (18)	50 (18)
C	13 (3)	9 (3)
CD4 count — cells/mm ³		
Median (range)	363 (2–646)	363 (2–630)
Interquartile range	281–448	280–444
HIV-1 RNA level — copies/ml		
Median	37,075	39,000
Mean	40,027	40,713
Mean log ₁₀	4.5±0.4	4.5±0.3

*Details of the disposition of patients included but not randomly assigned to a group are given in the Results section. Plus-minus values are means ±SD. Four patients at base line and two patients at the time of randomization each had two risk factors. CDC denotes Centers for Disease Control and Prevention. Because of rounding, percentages do not always total 100.

milliliter were reached by 84 percent of the patients whose HIV-1 RNA values at base line were below 30,000 copies per milliliter and by 64 percent of patients with base-line values of 30,000 or more per milliliter.

Duration of Follow-up and Study Treatment

The median follow-up period was six months after randomization (interquartile range, four to eight), with no significant difference among the treatment groups. Seven patients (3 percent) were lost to follow-up (loss to follow-up was defined by a period of more than three months since the last visit). Of the 279 patients randomly assigned to maintenance therapy, 8 (3 percent) discontinued the study treatment prematurely but were kept in the analysis (2 receiving zidovudine, lamivudine, and indinavir, 1 receiving zidovudine plus lamivudine, and 5 receiving zidovudine plus indinavir).

Primary End Point

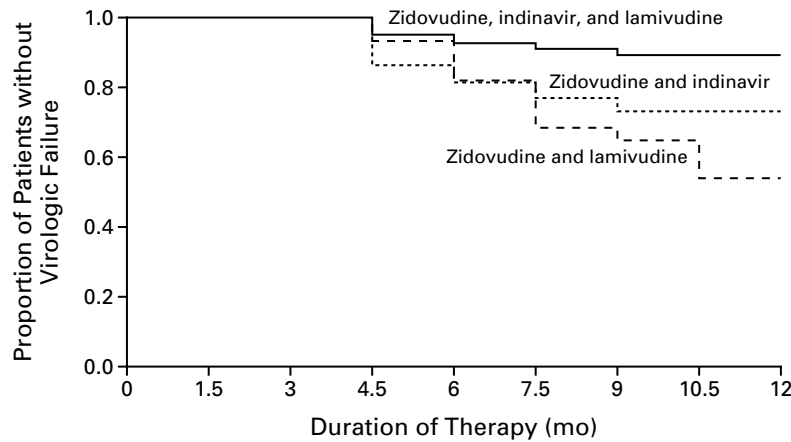
At the time of the review by the data and safety monitoring board, the primary end point had been reached in 44 patients (16 percent): 6 in the group receiving triple-drug therapy (7 percent), 16 in the zidovudine–indinavir group (17 percent), and 22 in the zidovudine–lamivudine group (24 percent). The primary end point was reached in a further 14 pa-

tients before December 31, 1997. The results presented in this report are therefore based on 58 virologic events and confirm the early recommendation of the data and safety monitoring board.

Virologic failure occurred in 29 patients receiving zidovudine plus lamivudine (31 percent) and 21 patients receiving zidovudine plus indinavir (22 percent), as compared with 8 patients receiving zidovudine, lamivudine, and indinavir (9 percent). Kaplan–Meier estimates showed that eight months after randomization, the probability of virologic failure was 46 percent (95 percent confidence interval, 31 to 64 percent) for patients receiving zidovudine plus lamivudine, 27 percent (95 percent confidence interval, 18 to 38 percent) for patients receiving zidovudine plus indinavir, and 11 percent (95 percent confidence interval, 5 to 20 percent) for patients receiving the three-drug regimen ($P<0.001$ and $P=0.01$, respectively, for the pairwise comparisons with the three-drug regimen) (Fig. 1).

There was no significant difference in the relative effects of the three treatments between patients with plasma HIV-1 RNA levels below 50 copies per milliliter and patients with 50 copies or more per milliliter at randomization. In the population with less than 50 copies per milliliter at randomization, virologic failure occurred in 17 patients receiving zidovudine plus lamivudine (27 percent), 12 patients receiving zidovudine plus indinavir (18 percent), and 2 patients receiving zidovudine, lamivudine, and indinavir (3 percent) ($P<0.001$ and $P<0.01$, respectively, for the pairwise comparisons with the three-drug combination, by the log-rank test) (Fig. 2A). In the population with 50 or more copies per milliliter at randomization, virologic failure occurred in 11 patients (48 percent) receiving zidovudine plus lamivudine, 7 patients (28 percent) receiving zidovudine plus indinavir, and 5 patients (3 percent) receiving zidovudine, lamivudine, and indinavir ($P=0.07$ and $P=0.46$, respectively, for the pairwise comparisons with the three-drug combination, by the log-rank test) (Fig. 2B).

The proportion of patients reaching the primary end point was significantly lower in the subgroup with less than 30,000 copies per milliliter at base line than in the subgroup with 30,000 or more copies per milliliter ($P<0.01$) (Fig. 3). In the latter subgroup, the P values for pairwise comparisons with the patients receiving three drugs were <0.001 for those receiving zidovudine plus lamivudine and 0.06 for those receiving zidovudine plus indinavir. In the subgroup with lower levels of HIV-1 RNA, in which the number of events was small, the results for the triple-drug regimen were not significantly different from those for either zidovudine plus lamivudine or zidovudine plus indinavir ($P=0.24$ and $P=0.08$, respectively), but the trend was consistent with the main results of the study.



NO. AT RISK						
	0	3	6	9	12	
Zidovudine, indinavir, and lamivudine	92	84	78	60	49	21
Zidovudine and lamivudine	93	89	83	55	37	12
Zidovudine and indinavir	94	88	73	53	42	21

Figure 1. Kaplan–Meier Estimates of the Proportion of All 279 Patients Randomly Assigned to Maintenance Therapy in Whom the Primary Study End Point of Virologic Failure Was Not Reached. P=0.002 for the comparison among the three regimens by the log-rank test with 2 df. Randomization occurred at three months.

Changes in CD4 Cell Counts

A sustained increase in CD4 cell counts above baseline values was seen in all three groups (data not shown). At the end of the three-month induction period, the mean increase in the CD4 cell count was 85 per cubic millimeter, and there was no statistical difference among the three groups at randomization. From randomization to month 9, the mean CD4 cell count in the patients assigned to the three-drug regimen, zidovudine plus lamivudine, and zidovudine plus indinavir increased by 53, 59, and 73 per cubic millimeter, respectively (P=0.69 for zidovudine plus lamivudine, and P=0.15 for zidovudine plus indinavir, as compared with the three-drug regimen).

Biologic Predictors of the Primary End Point

In the univariate analysis, the plasma level of HIV-1 RNA at base line and at randomization (below 50 or between 50 and 500 copies per milliliter) and the CD4 cell count at randomization were significantly associated with the risk of subsequent virologic failure. In the multivariate analysis, the value of plasma HIV-1 RNA at base line, but not the value at randomization or the change in the CD4 cell count from base line to randomization, was significantly associated with the risk of virologic failure. At base line, a value for HIV-1 RNA that was 1.0 log₁₀ copy per milliliter lower was associated with a decrease in risk of 78 percent (Table 2).

Adverse Events and Compliance

During the induction phase, 46 adverse clinical or biologic events were observed in 35 patients. The most common were nephrolithiasis and gastrointestinal disturbances.

During the maintenance phase, 23 clinical and biologic adverse events were observed in 20 patients. Three percent of patients receiving the triple-drug regimen had one or more severe clinical adverse events, as compared with 5 percent of those receiving zidovudine plus lamivudine and 3 percent of those receiving zidovudine plus indinavir (P=0.49 and P=0.98, respectively, for the comparison with the triple-drug regimen). The proportion of patients with severe laboratory abnormalities was 2 percent in the group receiving the triple-drug regimen, 5 percent in the group receiving zidovudine plus lamivudine, and 5 percent in the group receiving zidovudine plus indinavir (P=0.25 and P=0.16, respectively, as compared with the triple-drug regimen). There were no significant differences among the three maintenance groups in terms of the ratio between the number of days of full compliance and the number of planned treatment days.

DISCUSSION

A combination of two nucleoside analogues and a protease inhibitor drives plasma HIV-1 RNA concentrations below the limit of detection in 60 to 90

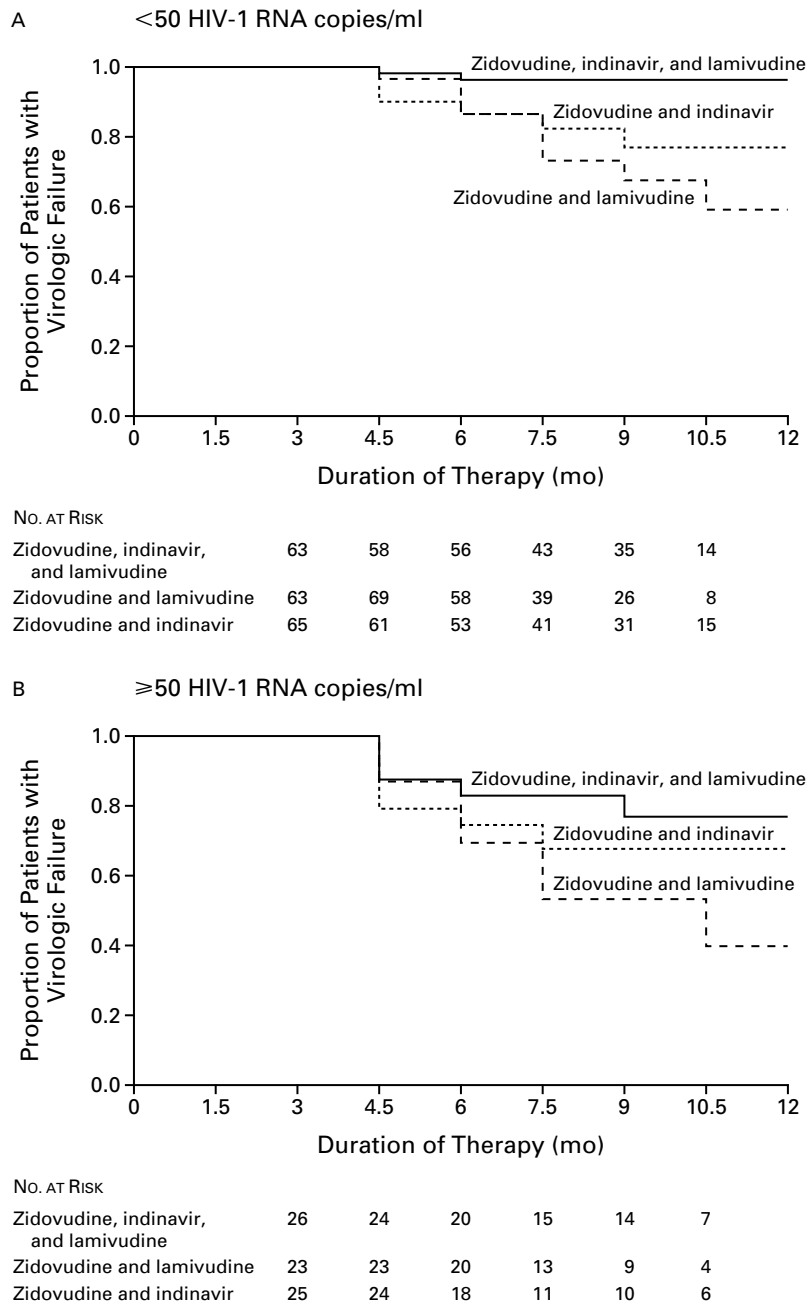


Figure 2. Kaplan–Meier Estimates of the Proportion of Patients in Whom the Primary Study End Point of Virologic Failure Was Not Reached, According to Plasma Levels of HIV-1 RNA at the Time of Randomization to Maintenance Therapy.

Panel A shows estimates for 191 patients with less than 50 copies of HIV-1 RNA per milliliter of plasma at the time of randomization to maintenance therapy, at three months ($P=0.002$ by the log-rank test with 2 df), and Panel B shows estimates for 74 patients with 50 or more copies ($P=0.20$ by the log-rank test with 2 df). Blood-test results were missing for 14 patients.

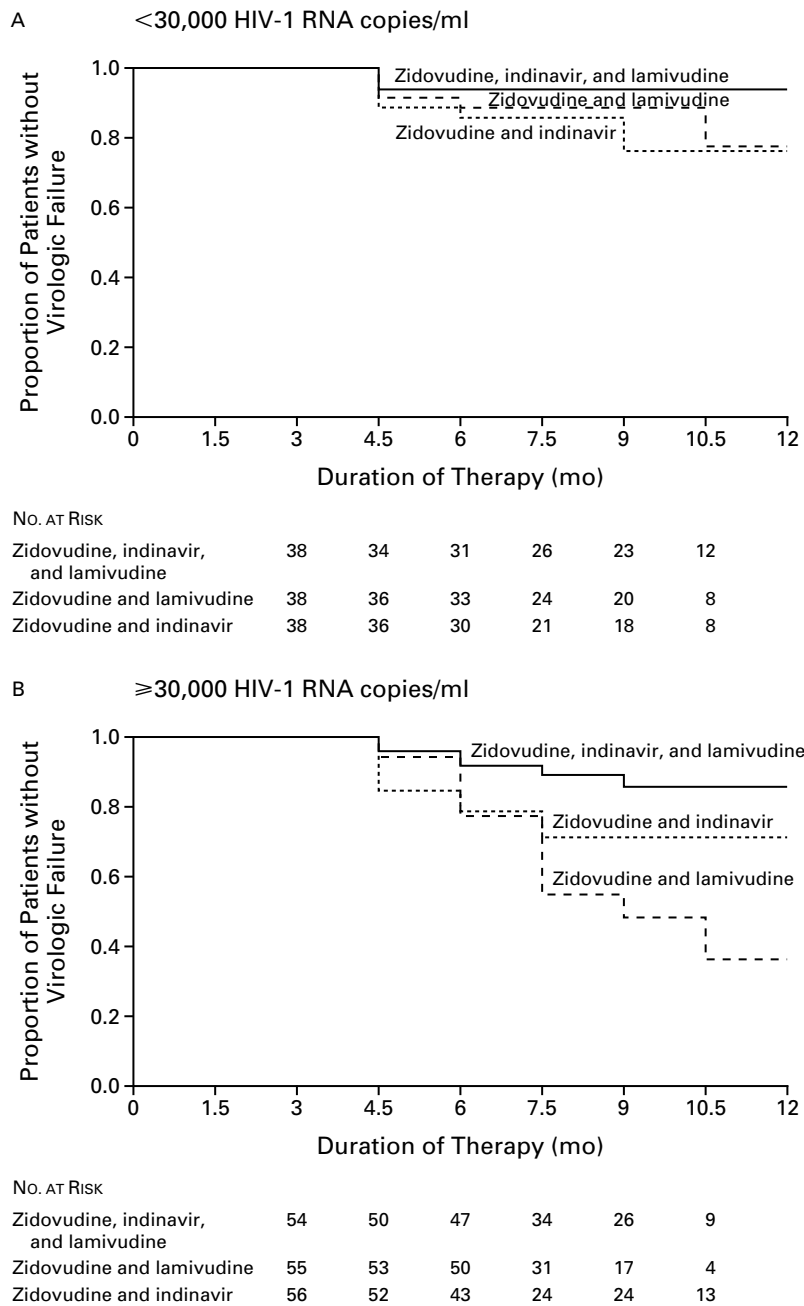


Figure 3. Kaplan–Meier Estimates of the Proportion of Patients in Whom the Primary Study End Point of Virologic Failure Was Not Reached, According to Plasma Levels of HIV-1 RNA at Base Line.

Panel A shows estimates for 114 patients with less than 30,000 copies of HIV-1 RNA per milliliter of plasma at base line, at the beginning of induction therapy ($P=0.22$ by the log-rank test with 2 df), and Panel B shows estimates for 165 patients with 30,000 or more copies ($P=0.002$ by the log-rank test with 2 df). Randomization occurred at three months.

TABLE 2. UNIVARIATE AND MULTIVARIATE PROPORTIONAL-HAZARDS MODELS FOR PREDICTING VIROLOGIC FAILURE.*

TIME AND VARIABLE	UNIVARIATE		MULTIVARIATE	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
At base line				
CD4 cell count†	0.82 (0.66–1.02)	0.07	0.85 (0.68–1.06)	0.15
HIV-1 RNA value‡	0.20 (0.08–0.53)	0.001	0.22 (0.08–0.63)	0.005
At randomization				
HIV-1 RNA level (<50 vs. ≥50 copies/ml)	0.49 (0.28–0.84)	0.01	0.68 (0.38–1.21)	0.19
CD4 cell count, change from base line†	0.94 (0.75–1.17)	0.58	0.90 (0.69–1.15)	0.39
CD4 cell count‡	0.83 (0.69–1.00)	0.05	—	—

*CI denotes confidence interval.

†The hazard ratios are those associated with an increase of 100 cells per cubic millimeter in the base-line CD4 cell count.

‡The hazard ratios are those associated with a decrease of 1.0 in the value for HIV-1 RNA, expressed in log₁₀ copies per milliliter.

percent of patients.^{4,5} In this study, the plasma level of HIV-1 RNA was reduced to below 500 copies per milliliter after eight weeks of therapy in 86 percent of previously untreated patients receiving zidovudine, lamivudine, and indinavir.

These complex regimens are associated with problems of compliance and toxicity.^{17,18} We therefore examined whether a two-drug regimen (zidovudine plus either lamivudine or indinavir) could maintain the viral suppression (indicated by an undetectable viral load) achieved during an aggressive induction phase with the triple-drug combination. We used a three-month induction phase, with two objectives: to achieve an undetectable level of plasma HIV-1 RNA in a high percentage of patients, and to limit the risks of side effects, poor compliance, and viral resistance associated with a prolonged exposure to triple-drug induction therapy.

The relapse rate eight months after randomization was clearly lower in the group remaining on triple-drug therapy (11 percent, as compared with 46 percent among those receiving zidovudine plus lamivudine and 27 percent among those receiving zidovudine plus indinavir; $P < 0.001$ and $P = 0.01$, respectively). The differences were significant among the patients with 30,000 copies of HIV-1 RNA or more per milliliter at base line. There was a similar trend among those with lower levels of HIV-1 RNA. The relapses were not restricted to the first few weeks of the maintenance phase but were observed throughout follow-up. In view of these results, the trial was prematurely terminated. It is conceivable, however, that a different trial design might have produced different results. For example, longer and more aggressive initial therapy in patients with a lower base-line viral load and different maintenance regimens might

have resulted in a lower rate of virologic failure during the maintenance phase.

The CD4 cell count and plasma HIV-1 RNA level were determined at base line (the beginning of induction therapy) and three months later (the beginning of maintenance therapy), but only a higher base-line plasma HIV-1 RNA level was an independent predictor of virologic failure in a multivariate proportional-hazards model. Interestingly, in this multivariate model, a plasma HIV-1 RNA level of less than 50 copies per milliliter at three months was not independently associated with a significantly lower risk of virologic failure during maintenance therapy. Thus, when treatment was reduced after three months of aggressive induction therapy, there was no long-term benefit associated with an initial decrease of the plasma viral load to less than 50 copies per milliliter.

Although severe adverse events occurred in 35 patients (9 percent) during the induction phase, only a few patients discontinued treatment because of adverse events during the maintenance phase. The rate of serious adverse events was low and did not differ significantly among the three groups. Data on compliance, collected by the site investigators, did not differ significantly among the treatment groups. Since recent data on viral dynamics during therapy, including the identification of a reservoir of replication-competent virus in long-lived memory CD4 T cells,^{15,16} suggest that eradication of virus is not yet a realistic target with the drugs currently available, intensive long-term treatment appears highly desirable. Because side effects and lack of compliance are major obstacles to prolonged therapy with highly active antiretroviral drugs, a continued search for alternative strategies is warranted. The induction–main-

tenance strategy, in which one of the three drugs in the initial regimen is withdrawn, was not virologically successful in this trial and in another study.²¹ However, the results should not be interpreted to indicate that a different maintenance regimen, or a longer induction period with the same maintenance regimen, is unlikely to be effective. Until the results of other trials are available, the induction-maintenance strategy cannot be recommended.

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APPENDIX

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