

# The New England Journal of Medicine

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Volume 333

AUGUST 17, 1995

Number 7

## A COMPARISON OF IMMEDIATE WITH DEFERRED ZIDOVUDINE THERAPY FOR ASYMPTOMATIC HIV-INFECTED ADULTS WITH CD4 CELL COUNTS OF 500 OR MORE PER CUBIC MILLIMETER

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**Abstract Background.** *The clinical benefits of zidovudine remain unproved in patients with asymptomatic human immunodeficiency virus (HIV) infection when CD4 cell counts exceed 500 per cubic millimeter. We compared zidovudine therapy given immediately with deferred therapy in such subjects.*

**Methods.** *Beginning in 1987, subjects with asymptomatic HIV infection and 500 or more CD4 cells per cubic millimeter were randomly assigned to receive placebo or zidovudine (either 500 or 1500 mg per day, starting immediately). In 1989, the study was modified so that open-label treatment with 500 mg of zidovudine per day (deferred therapy) was offered when CD4 cell counts fell below 500 per cubic millimeter. The study end points included overall survival, survival free of the acquired immunodeficiency syndrome (AIDS), toxic effects, and changes in CD4 cell counts.*

**Results.** *There were 1637 subjects who could be evaluated: 547 in the deferred-therapy group, 549 in the group receiving 500 mg of zidovudine immediately, and 541 in the 1500-mg group. The subjects were followed for*

*up to 6.5 years (group medians, 4.8, 4.8, and 4.9, respectively). There was no significant difference in AIDS-free survival in the deferred-therapy group as compared with the low-dose or high-dose groups (81 cases of progression to AIDS or death vs. 81 and 74, respectively;  $P=0.95$  and  $P=0.13$ ) or in overall survival (51 deaths vs. 47 and 46;  $P=0.25$  and  $P=0.16$ ). The decline in CD4 cells was slower in both immediate-therapy groups than in the deferred-therapy group ( $P<0.001$  for both). Adverse effects were uncommon, and before the study modification their incidence was similar among the treatment groups, but severe anemia and granulocytopenia were more frequent in the 1500-mg group than in the deferred-therapy group ( $P<0.001$ ).*

**Conclusions.** *In asymptomatic, HIV-infected adults with 500 or more CD4 cells per cubic millimeter, treatment with zidovudine slows the decline in the CD4 cell count but does not significantly prolong either AIDS-free or overall survival. These results do not encourage the routine use of zidovudine monotherapy in this population. (N Engl J Med 1995;333:401-7.)*

ZIDOVUDINE monotherapy is an effective treatment for symptomatic human immunodeficiency virus (HIV) disease, but its use in persons with asymptomatic infection remains controversial. Zidovudine therapy has been associated with a slowing in the clinical progression of disease and with longer survival in patients with the acquired immunodeficiency syndrome

(AIDS) or AIDS-related complex.<sup>1</sup> In patients with mildly symptomatic HIV disease, zidovudine slowed the rate of progression to more severe stages of disease.<sup>2,3</sup> In 1990, the drug was shown to slow the clinical progression to AIDS substantially in persons with asymptomatic HIV infection and fewer than 500 CD4 cells per cubic millimeter.<sup>4</sup> In the prolonged follow-up of that study, zidovudine was associated with a slower progression to AIDS for a period of more than two years, but therapy instituted earlier during asymptomatic infection did not prolong survival additionally.<sup>5</sup>

The results of several trials of zidovudine monotherapy in earlier stages of HIV disease may appear inconsistent. In one placebo-controlled trial in which the majority of subjects had CD4 cell counts between 500 and 750 per cubic millimeter, zidovudine had a clinical benefit, but the study end points included the development of mild and somewhat subjectively defined symptoms or a decline in the CD4 count.<sup>6</sup> In another trial, in

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Supported by grants (AI 27763 and AI 27663) from the National Institute of Allergy and Infectious Diseases (NIAID) and by the NIAID Clinical Trials Group.

\*The institutions and investigators participating in the AIDS Clinical Trials Group are listed in the Appendix.

which 42 percent of subjects had CD4 cell counts above 500 per cubic millimeter, there was no overall benefit in terms of a slower progression to AIDS or longer survival (median follow-up, three years).<sup>7</sup> In view of these results, interest continues in antiretroviral therapies for HIV-infected persons with CD4 cell counts of 500 per cubic millimeter or higher, particularly since there is active viral proliferation during all stages of disease.<sup>8,9</sup>

The AIDS Clinical Trials Group (ACTG) protocol 019 was designed and begun in 1987 as two separate studies, one of subjects with base-line CD4 cell counts below 500 per cubic millimeter and a second of subjects with base-line counts of 500 per cubic millimeter or above. Both studies were initially designed to be straightforward controlled comparisons of two dosages of zidovudine (500 mg and 1500 mg per day) with placebo, with respect to the progression of AIDS, severe AIDS-related complex, or death. In 1989, the study — reported here — of the subjects with higher base-line CD4 cell counts was continued, but was modified because a significant prolongation of AIDS-free survival was found in subjects with fewer than 500 cells per cubic millimeter who received zidovudine.<sup>4</sup> In this modification, subjects whose CD4 cell counts fell below 500 per cubic millimeter were offered open-label treatment with 500 mg of zidovudine per day, a study design that permitted therapy given immediately on enrollment to be compared with deferred therapy. We followed all the subjects prospectively to learn of the development of AIDS or death.

## METHODS

### Patient Population, Study Design, and Criteria for a Response

This study was a multicenter, three-group, randomized, double-blind trial involving asymptomatic, HIV-infected subjects with CD4 cell counts of 500 per cubic millimeter or higher. Apart from the CD4 cell count, the criteria for enrollment were the same as in the earlier trial.<sup>4</sup> Both studies were designed to compare placebo with zidovudine monotherapy (500 mg or 1500 mg per day, given in divided doses) until the occurrence of advanced AIDS-related complex, AIDS, or death. The protocol was modified in August 1989 so that open-label therapy with 500 mg of zidovudine per day was offered to all subjects whose CD4 cell counts fell below 500 per cubic millimeter. Recipients of placebo whose CD4 cell counts fell below 500 per cubic millimeter before the time of the modification were immediately offered open-label zidovudine in August 1989; subjects assigned to zidovudine whose counts fell below 500 per cubic millimeter continued to receive their initial dosage of zidovudine in blinded fashion until March 1990, when they were all offered open-label zidovudine (500 mg daily). Open-label zidovudine was not offered to subjects who had discontinued blinded therapy before August 1989. As in other ACTG trials, the modified study design no longer used AIDS-related complex as an end point because of difficulty in documenting that event reliably. Thus, whereas the original design compared two dosages of zidovudine with placebo with respect to clinical progression, the modified design compared zidovudine given immediately with therapy that was deferred until the CD4 cell count fell below 500 per cubic millimeter. Most of the study data were obtained after the implementation of this modified design, because the change was made relatively early in the trial. Specifically, among the subjects randomly assigned to receive placebo, only 8.7 percent of the total follow-up was spent receiving placebo after their CD4 cell counts fell below 500 per cubic millimeter (i.e., time spent following the original study design). Thus, the results of the trial

were overwhelmingly driven by the study design comparing immediate zidovudine therapy with deferred therapy.

The primary end point in the study of efficacy was the progression to AIDS (as defined in 1987 by the Centers for Disease Control) or death. After November 1988, the definition of this end point was modified to include AIDS dementia complex, but not the HIV wasting syndrome. Each end point was reviewed by a data manager and the study chairperson without knowledge of the subject's treatment assignment. Secondary end points were toxic effects and changes in CD4 cell counts. All the subjects gave written informed consent, and the study design was approved by the institutional review board at each site.

### Evaluation and Follow-up of Subjects

The subjects were seen every 2 weeks for the first 16 weeks, and every 4 weeks thereafter. After the CD4 cell count obtained to determine eligibility, additional counts were obtained at entry into the study and at week 8, week 16, and every 16 weeks thereafter. Routine laboratory testing, which included complete blood counts and evaluations of renal and hepatic function in addition to the CD4 cell counts, was performed only while the subjects were receiving blinded treatment or open-label therapy. The subjects were studied monthly for the occurrence of end points until July 1990, when for convenience the interval between visits was increased to every three months for the subjects receiving open-label zidovudine and those who had permanently discontinued the study therapy.

### Statistical Analysis

The subjects were randomly assigned to the three treatment groups in equal numbers with the use of permuted blocks at each participating center. Cox regression models and Kaplan–Meier curves were used to assess the duration of AIDS-free survival and overall survival and the time needed for the CD4 cell count to decline to specified levels (500, 400, and 300 cells per cubic millimeter). The randomized treatment groups were compared with respect to the clinical progression of disease and survival on the basis of the Cox regression model  $RR(t) = \exp\{B_1 + B_2 \times t\}$ , where  $RR(t)$  is the relative risk for immediate as compared with deferred zidovudine  $t$  years after randomization and  $B_1$  and  $B_2$  are the regression parameters estimated from the data. The null hypothesis of no difference between treatment groups was given by the formula  $B_1 = B_2 = 0$  and was assessed with the likelihood-ratio test from the Cox regression model, with two degrees of freedom. This form of the Cox model gave the study greater power to detect nonproportional differences between treatments than the usual form, which excludes the term involving  $B_2$ . Changes in CD4 cell counts in subjects with counts above 650 cells per cubic millimeter, the approximate median count at entry into the study, and subjects with counts of 650 cells per cubic millimeter or fewer, were analyzed separately with the usual form of the Cox model, as a secondary end point, in order to determine the consistency of the overall results according to the base-line CD4 cell count. Fisher's exact test was used both to test for group differences in the incidence of severe adverse effects and symptoms and with the Kruskal–Wallis test, to assess the homogeneity of base-line characteristics among treatment groups. All analyses of efficacy were performed on an intention-to-treat basis in that they included the available information on all subjects who could be evaluated. All  $P$  values were two-sided.

Five scheduled interim analyses of the study were presented to the Data and Safety Monitoring Board of the National Institute of Allergy and Infectious Diseases. The study ended as planned in January 1994.

## RESULTS

### Enrollment and Eligibility of Subjects and Characteristics at Entry

A total of 1650 subjects were enrolled in the study between July 1987 and July 1989 at 32 sites. Thirteen subjects were excluded from the final analysis, five, two, and six of whom were in the deferred-therapy, the

500-mg, and the 1500-mg groups, respectively. Four subjects had major violations of the criteria for entry into the study: three were found to be HIV-negative at entry, and one had Kaposi's sarcoma before randomization. Nine others were either randomized inadvertently or found to be ineligible and lost to follow-up immediately after randomization. Of the 1637 subjects who could be evaluated, 547, 549, and 541 were in the deferred-therapy group, the 500-mg group, and the 1500-mg group, respectively.

The subjects were predominantly white men (90 percent), homosexual (69 percent), and non-Hispanic (89 percent); they had a median age of 33 years at entry. Ten percent indicated that they had used drugs parenterally since 1978. The median base-line CD4 cell count was 655 per cubic millimeter. The three treatment groups were well balanced with respect to all characteristics measured at base line.

#### Duration of Follow-up and Treatment

The subjects were followed until the end of the study to detect the end points of progression to AIDS or death. The longest period of follow-up was 6.5 years, with medians of 4.8, 4.8, and 4.9 years, respectively, in the deferred-therapy, the 500-mg, and the 1500-mg groups. There was a total of 6850 person-years of follow-up for progression to the clinical end points. The patients' treatment histories are summarized in Table 1. Twenty-eight subjects (2 percent) never started treatment but were included in all the analyses (Table 2). Of the 963 subjects who began randomized therapy but never received open-label zidovudine, 591 (61 percent) voluntarily discontinued their assigned therapy, 216 (22 percent) were still being treated in blinded fashion when the study ended, 59 (6 percent) were withdrawn from the study medication because of adverse effects, 37 (4 percent) reached a study end point, and 60 (6 percent) withdrew for other reasons. Of the 1609 subjects who began treatment, a total of 646 (40 percent) began receiving open-label zidovudine. The median times spent receiving blinded and open-label treatment are shown in Table 1.

#### Voluntary Withdrawal from Treatment and Loss to Follow-up

Of the 1609 subjects who started treatment, 591 (37 percent) voluntarily discontinued the study drug while receiving blinded treatment and 353 (22 percent) voluntarily discontinued treatment during the open-label portion of the study (when all three groups received zidovudine). The rates of discontinuation were 16.9 per 100 person-years of follow-up during the blinded portion of the study and 19.6 per 100 person-years during the overall study. In all, 39 percent of discontinuations occurred within the first year after randomization. The most commonly reported reasons for withdrawal were the desire to receive another drug or participate in another trial (391 subjects) and noncompliance with respect to appointments or medications (393 subjects). Only 11 percent reported discontinuing treatment because of an adverse effect not defined in the protocol.

Table 1. Treatment Histories of the Study Subjects According to Assigned Zidovudine Regimen.

| VARIABLE*                                 | DEFERRED THERAPY | IMMEDIATE THERAPY |         | ALL SUBJECTS |
|---|------------------|-------------------|---------|--------------|
|   |                  | 500 mg            | 1500 mg |              |
| No. who could be evaluated                | 547              | 549               | 541     | 1637         |
| Blinded treatment                         |                  |                   |         |              |
| No. who started                           | 537              | 543               | 529     | 1609         |
| Median duration (yr)                      | 1.4              | 1.7               | 1.7     | 1.6          |
| Reasons for termination                   |                  |                   |         |              |
| End of study                              | 49               | 84                | 83      | 216          |
| Protocol-defined toxicity                 | 11               | 18                | 30      | 59           |
| AIDS or ARC                               | 13               | 13                | 4       | 30           |
| Death                                     | 2                | 2                 | 3       | 7            |
| Voluntary discontinuation                 | 197              | 200               | 194     | 591          |
| Other                                     | 22               | 16                | 22      | 60           |
| Open-label treatment                      |                  |                   |         |              |
| No. who started                           | 243              | 210               | 193     | 646          |
| Median duration (yr)                      | 2.2              | 2.0               | 1.8     | 1.9          |
| Reasons for termination                   |                  |                   |         |              |
| End of study                              | 81               | 64                | 58      | 203          |
| Protocol-defined toxicity                 | 4                | 1                 | 3       | 8            |
| AIDS or ARC                               | 20               | 19                | 14      | 53           |
| Death                                     | 2                | 1                 | 1       | 4            |
| Voluntary discontinuation                 | 126              | 114               | 113     | 353          |
| Other                                     | 10               | 11                | 4       | 25           |
| Median overall duration of treatment (yr) | 2.2              | 3.3               | 3.3     | 2.9          |

\*Data on the duration of zidovudine treatment are for all subjects who began the treatment. ARC denotes AIDS-related complex.

Rates of voluntary discontinuation did not differ significantly among the three groups, either while CD4 cell counts were 500 per cubic millimeter or higher ( $P=0.36$  by log-rank test) or overall ( $P=0.60$ ). However, the subjects who withdrew voluntarily had somewhat steeper rates of decline in their CD4 cell counts than the subjects who continued receiving their treatment.

A total of 569 subjects (35 percent) were lost to follow-up during the study (Table 2), at rates of 8.9, 8.0,

Table 2. Reasons for the Termination of Follow-up to Detect the Progression to AIDS or Death, According to Assigned Zidovudine Regimen.

| VARIABLE*                              | DEFERRED THERAPY | IMMEDIATE THERAPY |         |
|--|------------------|-------------------|---------|
|  |                  | 500 mg            | 1500 mg |
| No. who could be evaluated             | 547              | 549               | 541     |
| No. who later had AIDS or died         | 81               | 81                | 74      |
| Never started treatment                | 1                | 1                 | 0       |
| During blinded treatment               | 10               | 13                | 7       |
| During time off blinded treatment      | 20               | 23                | 25      |
| During open-label treatment            | 19               | 20                | 16      |
| After terminating open-label treatment | 31               | 24                | 26      |
| No. unavailable for follow-up†         | 200              | 186               | 183     |
| Never started treatment                | 6                | 5                 | 9       |
| During blinded treatment               | 55               | 48                | 53      |
| During time off blinded treatment      | 93               | 89                | 91      |
| During open-label treatment            | 20               | 21                | 19      |
| After terminating open-label treatment | 26               | 23                | 11      |
| No. who completed study                | 266              | 282               | 284     |
| Never started treatment                | 3                | 0                 | 3       |
| During blinded treatment               | 49               | 85                | 82      |
| During time off blinded treatment      | 67               | 75                | 78      |
| During open-label treatment            | 75               | 60                | 56      |
| After terminating open-label treatment | 72               | 62                | 65      |
| Median follow-up (yr)                  | 4.8              | 4.8               | 4.9     |

\*Numbers of patients shown during blinded or open-label treatment include those whose treatment had terminated within the preceding 30 days.

†AIDS had not yet developed in these patients.

and 8.0 per 100 person-years of follow-up in the deferred-therapy, the 500-mg, and the 1500-mg groups, respectively. These rates did not differ significantly among the three groups ( $P=0.44$  by the log-rank test).

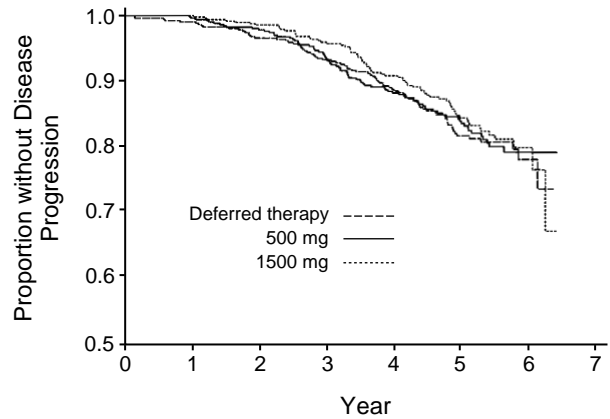
**Clinical Progression of Disease and Survival**

Among the 236 subjects (14 percent of the overall group of 1637) who progressed to AIDS or died during follow-up, 187 had AIDS as their first event, and 49 died without a diagnosis of AIDS (Table 3). Table 2 shows the relation between the study end points and the patients' treatment histories. A total of 151 events (64 percent) occurred 30 or more days after the patients had discontinued the study treatment, including 2 events in subjects who never started the study therapy. The most common disorders leading to the diagnosis of AIDS were *Pneumocystis carinii* pneumonia (65 cases), Kaposi's sarcoma (33 cases), and cytomegalovirus infection (24 cases), and the incidence of these diagnoses did not differ among treatment groups.

The clinical experiences of the subjects are shown in Table 3 according to treatment group. Figure 1 shows the corresponding Kaplan–Meier analysis of the distribution of times to disease progression. Neither the 500-mg nor the 1500-mg group had significantly longer AIDS-free survival than the deferred-therapy group ( $P=0.95$  and  $P=0.13$ , respectively).

Among the 144 deaths, 95 occurred after the development of AIDS. In 134 cases, death occurred long after the discontinuation of the study therapy (median, 1.5 years). The death rates in the deferred-therapy, 500-mg, and 1500-mg groups were 2.2, 1.9, and 2.0 per 100 person-years of follow-up, respectively (Fig. 2). These differences were not statistically significant ( $P=0.25$  and  $P=0.16$ , respectively, for the comparison of the 500-mg and 1500-mg groups with the deferred-therapy group).

Additional analyses of AIDS-free and overall survival compared the treatment groups separately according



| GROUP            |     |     |     |     |     |     |    |
|------------------|-----|-----|-----|-----|-----|-----|----|
| Deferred therapy | 547 | 493 | 444 | 406 | 355 | 223 | 35 |
| 500 mg           | 549 | 503 | 470 | 422 | 371 | 248 | 49 |
| 1500 mg          | 541 | 490 | 456 | 424 | 371 | 245 | 39 |

Figure 1. Kaplan–Meier Estimates of the Progression to AIDS or Death, According to Treatment Group.

The number of subjects in the analysis each year is shown below the graph.

to base-line CD4 cell counts ( $\leq 650$  or  $>650$  cells per cubic millimeter), using the usual form of the Cox model, which assumes a constant relative risk, and by controlling for the base-line CD4 count in the Cox model. In each case, the results did not differ significantly among treatment groups.

**Changes in CD4 Cell Counts**

CD4 cell counts were determined a median of 12 times. The top panel in Figure 3 shows how much time elapsed before the first count in each subject fell below 500 per cubic millimeter. The median interval was approximately 1.5 years in the immediate-therapy (500-mg and 1500-mg) groups and 1.0 year in the deferred-therapy group — a significant difference when the immediate-therapy groups were compared with the deferred-therapy group ( $P<0.001$  by the log-rank test).

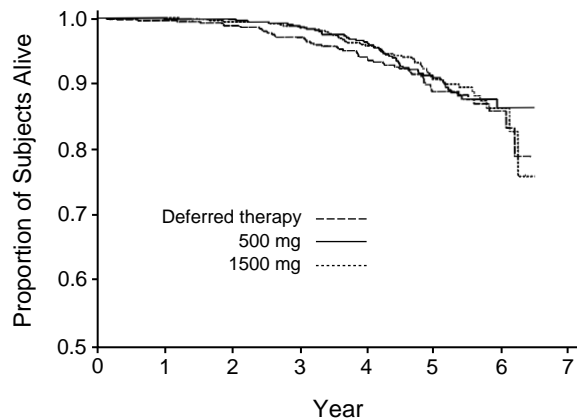
In subjects with 650 or fewer CD4 cells per cubic millimeter at base line, immediate therapy with zidovudine delayed the time needed for the count to fall below 500 cells by approximately six months (Fig. 3, middle panel), yet each group reached that level in a median time of less than one year. In contrast, the median time that elapsed before the CD4 cell count fell below 500 per cubic millimeter was much greater in the group with initial counts above 650 per cubic millimeter (Fig. 3, bottom panel), and the effect of immediate zidovudine therapy was

Table 3. Progression to AIDS or Death in the Study Subjects According to Treatment Group.

| VARIABLE*                              | DEFERRED THERAPY (N = 547) | IMMEDIATE THERAPY |                   |                 |
|--|----------------------------|-------------------|-------------------|-----------------|
|  |                            | 500 mg (N = 549)  | 1500 mg (N = 541) | BOTH (N = 1090) |
| <b>Progression to AIDS or death</b>    |                            |                   |                   |                 |
| First clinical event — no. of subjects | 81                         | 81                | 74                | 155             |
| AIDS                                   | 59                         | 70                | 58                | 128             |
| Death                                  | 22                         | 11                | 16                | 27              |
| Event rate                             | 3.6                        | 3.5               | 3.2               | 3.4             |
| Relative risk (95% CI)                 | 1.00                       | 0.96 (0.7–1.3)    | 0.88 (0.64–1.2)   | 0.92 (0.7–1.2)  |
| P value†                               | —                          | 0.95              | 0.13              | 0.43            |
| <b>Death</b>                           |                            |                   |                   |                 |
| No. who died                           | 51                         | 47                | 46                | 93              |
| Mortality rate                         | 2.2                        | 1.9               | 1.95              | 1.9             |
| Relative risk (95% CI)                 | 1.00                       | 0.87 (0.6–1.3)    | 0.87 (0.6–1.3)    | 0.87 (0.6–1.2)  |
| P value†                               | —                          | 0.25              | 0.16              | 0.10            |

\*Event and mortality rates shown are per 100 person-years of observation. Relative risks were calculated from the Cox regression model, with the deferred-therapy group used as the reference category. CI denotes confidence interval.

†P values are for the comparison with the deferred-therapy group and were derived from the Cox regression model as described in the Methods section.



| GROUP            |     |     |     |     |     |     |    |
|------------------|-----|-----|-----|-----|-----|-----|----|
| Deferred therapy | 547 | 497 | 455 | 425 | 376 | 241 | 40 |
| 500 mg           | 549 | 507 | 485 | 451 | 407 | 268 | 55 |
| 1500 mg          | 541 | 491 | 460 | 436 | 393 | 265 | 42 |

Figure 2. Kaplan–Meier Estimates of the Proportion of Subjects Who Survived, According to Treatment Group.

The number of subjects in the analysis each year is shown below the graph.

more substantial, with a difference of approximately 1.5 years between the immediate-therapy groups and the deferred-therapy group ( $P < 0.001$ ).

Similarly, the CD4 cell counts in the immediate-therapy groups declined more slowly than those of the deferred-therapy group to less than 400 per cubic millimeter ( $P = 0.008$  and  $P < 0.001$  for the 500-mg and the 1500-mg groups, respectively) and to less than 300 per cubic millimeter ( $P = 0.07$  and  $P < 0.001$ ).

#### Adverse Effects and Compliance with Medication

The overall rates of severe adverse effects (grade 3 or 4, measured both objectively and subjectively) were extremely low, with no significant differences between the subjects receiving placebo and those in the 500-mg group. The 1500-mg group had significantly higher incidences of severe anemia (hemoglobin,  $< 8$  g per deciliter) and granulocytopenia ( $< 750$  cells per cubic millimeter) than the recipients of placebo ( $P < 0.001$  for both), although the absolute rates of these adverse effects were still low (about 4 percent for anemia and 5.6 percent for granulocytopenia). When all events were included, whether they occurred during the blinded or the open-label portion of the study, the results were similar.

Medical symptoms were the primary reason given for withdrawal by 101 (11 percent) of the 944 subjects who withdrew from treatment voluntarily. Among these subjects, 19 were in the deferred-therapy group, 38 were in the 500-mg group, and 44 were in the 1500-mg group. The most common symptoms were nausea and vomiting, fatigue, aches and pains, fever, and headache.

Mean corpuscular red-cell volume was monitored regularly throughout the study. This value was elevated

in less than 10 percent of the subjects receiving placebo during the blinded treatment, whereas it was consistently elevated in the recipients of zidovudine.

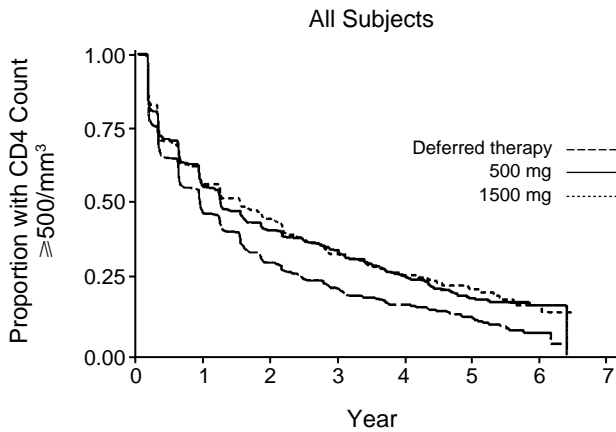
#### DISCUSSION

We found no additional clinical benefit from the immediate use of zidovudine in asymptomatic, HIV-infected subjects with 500 or more CD4 cells per cubic millimeter as compared with subjects who began to receive zidovudine only when their CD4 cell counts declined below 500 per cubic millimeter. This was the case despite a significant zidovudine-associated slowing in the decline of CD4 cell counts. Thus, routine zidovudine monotherapy in asymptomatic patients may not be justified as long as CD4 cell counts remain at 500 per cubic millimeter or above.

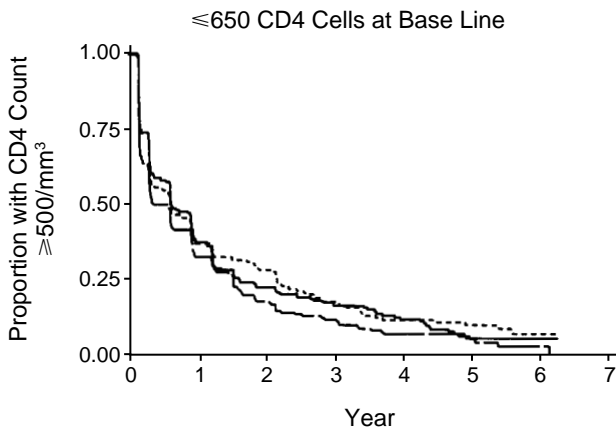
One may ask why the early use of zidovudine in this trial did not extend AIDS-free survival, even though this clinical benefit has been established in patients with more advanced disease and though there were significant beneficial effects on CD4 cell counts, which are an incomplete surrogate marker of the clinical benefit of zidovudine.<sup>10</sup> One possible explanation is that by the time there is a real risk of a clinical event, the CD4 cell count has generally fallen far below 500 per cubic millimeter, yet the treatments given in the trial differed only in the relatively brief period during which the counts remained above that level. Furthermore, even though the CD4 cell counts in the immediate-therapy groups took an average of six months more than those in the deferred-therapy group to fall below 500 per cubic millimeter, all three groups subsequently received open-label treatment for a much longer period (approximately two more years). Therefore, the experiences of the three groups during treatment were quite similar, and the opportunity for the earlier initiation of zidovudine treatment to affect the progression of disease was quite limited.

Second, there was a high rate of voluntary discontinuation of the assigned therapy (16.9 withdrawals per 100 person-years of follow-up) during the blinded phase of the study, when the treatments actually differed. These annual rates were somewhat lower than those in other antiviral studies.<sup>2,3,11,12</sup> Furthermore, they are likely to be similar to the rates observed in current clinical care, in which practice patterns and the compliance of patients change substantially over time. In an intention-to-treat analysis, these discontinuations (which occurred at similar rates in the three treatment groups) tend to reduce the power of the study to detect differences between treatments, and thus they could have masked a moderate effect of treatment.<sup>13</sup>

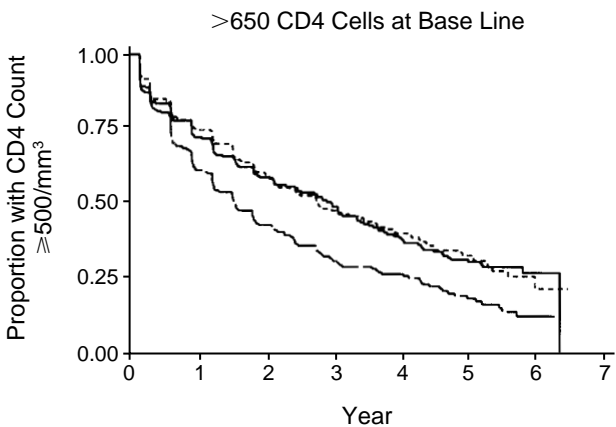
Finally, the apparent differences in CD4 cell counts between the treatment groups may themselves have been exaggerated, because these measurements were rarely obtained after a voluntary discontinuation of treatment, even though the clinical end points continued to be evaluated. Accordingly, the true CD4 cell counts of subjects assigned to immediate as compared with deferred zidovudine therapy who had reached a



| GROUP            |     |     |     |     |    |
|------------------|-----|-----|-----|-----|----|
| Deferred therapy | 541 | 183 | 109 | 72  | 52 |
| 500 mg           | 538 | 228 | 159 | 122 | 84 |
| 1500 mg          | 528 | 220 | 165 | 109 | 74 |



| GROUP            |     |    |    |    |    |
|------------------|-----|----|----|----|----|
| Deferred therapy | 271 | 64 | 33 | 19 | 10 |
| 500 mg           | 256 | 76 | 41 | 27 | 17 |
| 1500 mg          | 250 | 72 | 50 | 26 | 15 |



| GROUP            |     |     |     |    |    |
|------------------|-----|-----|-----|----|----|
| Deferred therapy | 270 | 119 | 76  | 53 | 42 |
| 500 mg           | 282 | 152 | 118 | 95 | 67 |
| 1500 mg          | 278 | 148 | 115 | 83 | 59 |

Figure 3. Kaplan–Meier Estimates of Changes in CD4 Cell Counts, According to Treatment Group and CD4 Cell Count at Base Line. The interval that elapsed before the CD4 cell count fell below 500 per cubic millimeter for the first time is shown for all subjects (top panel), for subjects with 650 or fewer CD4 cells per cubic millimeter at base line (middle panel), and for subjects with more than 650 CD4 cells per cubic millimeter at base line (bottom panel). The number of subjects in the analysis each year is shown below each graph.

clinical end point two to three years after discontinuing treatment may have been quite similar. If so, the apparent initial benefit of treatment on the CD4 count may not extend AIDS-free or overall survival significantly. Thus, we cannot exclude the possibility that zidovudine monotherapy is of some clinical benefit while CD4 cell counts are 500 or above, as compared with the later use of the drug. Indeed, the rates of progression to AIDS or death observed in the groups receiving early zidovudine therapy were slightly lower than those in the deferred-therapy group.

These results and those previously reported from the study conducted in subjects with lower base-line CD4 cell counts<sup>4</sup> represent a large and extended controlled clinical experience with zidovudine in HIV disease, as well as a robust examination of the optimal point at which this intervention should take place. In the two studies combined, there were 10,832 person-years of follow-up to detect clinical progression of disease. A statistically significant prolongation of AIDS-free survival was seen in the group with lower CD4 cell counts, whereas no clinical benefit was seen in the current study. It is, then, perhaps not surprising that the European Concorde study,<sup>7</sup> with half the follow-up of these combined trials, found no overall benefit when all the data on CD4 cell counts (both ≥ 500 and < 500 per cubic millimeter) were combined.

The design of future clinical trials must be altered if we are to continue to investigate drugs that have only moderate clinical activity in HIV-infected subjects when the subjects' risk of clinical progression is very low. The large size and long duration of conventional trials make them expensive and unwieldy, and the interpretation of their results and the strength of their conclusions are limited by the difficulties of maintaining consistency of treatment and compliance among subjects. Therefore, smaller studies using laboratory end points would be preferable, if clinical trials validate the use of direct viral or immunologic markers to gauge the effect of treatment.<sup>14</sup> Also, large trials that collect a minimum of data but use easily verifiable end points, such as mortality, may be of value in some instances for detecting small differences in outcomes.<sup>15</sup>

The recommendation from this controlled clinical trial in persons with asymptomatic HIV infection is that zidovudine monotherapy is not routinely indicated until the CD4 cell count declines below 500 per cubic millimeter. These results cannot necessarily be generalized to apply to symptomatic persons with high CD4 counts or those with acute HIV infection.

We are indebted to Karen Kazial, Anne Kmack, and Carol Suckow for their valuable contributions as the data managers of this study; to Donna Jacobsen and Claire Ong for their editorial assistance; to the many investigators, institutions, research staff members, and patients who participated in this trial; to the Burroughs Wellcome Company for providing zidovudine and placebo; and to the National Institute of Allergy and Infectious Diseases for its continued support of the many units of the AIDS Clinical Trials Group in which this work was conducted.

## APPENDIX

In addition to the principal study authors, the following persons and institutions participated in this trial, enrolled research subjects, or both. *University of California, San Francisco* — R. Coleman, K. Dybeck, and M. Jacobson; *University of California, San Diego* — D.D. Richman, S.A. Spector, and R. Snyder; *University of Miami, Miami* — D.T. Jayaweera, J. Patrone-Reese, and E. Dale; *University of Washington, Seattle* — D. Cummings, M. Paradise, and K. Huntington; *Northwestern University, Chicago* — H. Kessler, J. Pottage, and R. Murphy; *Harvard University, Boston* — C.S. Crumpacker, J.D. Allan, and S.E. Hussey; *University of California, Los Angeles* — S. Chafey, D. Duran, and G. Beall; *University of Minnesota, Minneapolis* — W.K. Henry, N.W. Reed, and S.E. Reaney; *University of Rochester, Rochester, N.Y.* — C. Greisberger, R. Hewitt, and D. Blair; *Albert Einstein College of Medicine, New York* — R. Soeiro, N. Steilbigel, C. Harris, and J. Schliussberg; *Ohio State University, Columbus* — M.F. Para, J.L. Neidig, R.J. Fass, and C. Jackson; *Johns Hopkins University, Baltimore* — J.G. Bartlett, J. Feinberg, R.L. Becker, and D.A. Wright; *Tulane University, New Orleans* — N. Hyslop, Jr., D.M. Mushatt, D. Hoadley, and J.A. Zachary; *Indiana University, Bloomington* — B. Zwickl and K. Fife; *Duke University Medical Center, Durham, N.C.* — J.A. Bartlett, A. Adinolfi, M. Packard, and C. Fowler; *Washington University, St. Louis* — W.G. Powderly, L.D. Gelb, M. Klebert, and J. Voorhees; *University of Southern California, Los Angeles* — J.M. Leedom, M.E. Liggins, P.D. Holtom, and N.R. Quesada; *New York University–Bellevue Hospital Center, New York* — V.J. McAuliffe, J. Funesti, J. Dowling, and F.T. Valentine; *George Washington University, Washington, D.C.* — D.M. Parenti and S. LeLacheur; *Georgetown University, Washington, D.C.* — P.F. Pierce and P.N. Kumar; *Case Western Reserve University, Cleveland* — J. Carey, M. Lederman, V.P. Jarrett, and C. Drain; *Robert Wood Johnson Medical School, New Brunswick, N.J.* — D.J. Gocke; *University of Pittsburgh, Pittsburgh* — M. Ho, D. McMahon, G. Pazin, and J. Armstrong; *University of Cincinnati, Cincinnati* — B. Wong, J. Brinkdopke, P. Daniel, and M. Hoelle; *Stanford University, Stanford, Calif.* — T.C. Merigan, Jr., D.A. Katzenstein, J. Fessel, and V.B. Tallman; *Mount Sinai Medical Center, New York* — H. Sacks, D. Mildvan, C. Sanders, and H. Mendoza; *St. Luke's–Roosevelt Hospital, New York* — G.F. McKinley, M.H. Grieco, J.A. Rivera, and J. O'Connor; *Memorial Sloan-Kettering Cancer Center, New York* — B. Polsky, D. Armstrong, D.E. Brown, and M.J. Nealon; *University of Massachusetts, Worcester* — S.H. Cheeseman, R.A. Koup, P.G. Fairchild, and K.K. Lai; *University of North Carolina, Chapel Hill* —

J. Eron, C. van der Horst, D. Ragan, and B. Longmire; *Cornell University, New York* — H.W. Murray, M.F. Giordano, J. Bowers, and L. Ponticello; *Milton S. Eisenhower Medical Center, Hershey, Pa.* — W.C. Ehmann, J. Zurlo, M. Kreher, D. Irwin, and R.T. Steigbigel; *State University of New York, Stony Brook* — R.A. Burk, R. Tenzler, and J. Fuhrer; *Data Management Center, Frontier Science, Inc., Amherst, N.Y.* — K. Kazial, A. Kmack, and C. Suckow; *Division of AIDS, National Institute of Allergy and Infectious Diseases, Rockville, Md.* — C. Pettinelli and A. Martinez; *ACTG Operations Office, Rockville, Md.* — J. Jermano, P. Clax, B. Bond, and P. Kasdan.

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