THE EFFECTS ON SURVIVAL OF EARLY TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

NEIL M.H. GRAHAM, M.B., B.S., M.D., M.P.H., SCOTT L. ZEGER, PH.D., LAWRENCE P. PARK, M.S.E., STEN H. VERMUND, M.D., PH.D., ROGER DETELS, M.D., M.S., CHARLES R. RINALDO, PH.D., AND JOHN P. PHAIR, M.D.*

Abstract Background. Zidovudine has been shown to prolong survival in patients with the acquired immunodeficiency syndrome (AIDS) and, in persons with human immunodeficiency virus (HIV) infection but not AIDS, to delay the progression to AIDS. However, it is still uncertain whether treatment before the development of AIDS prolongs survival.

Methods. We analyzed data from a cohort of 2162 high-risk men who were already seropositive for HIV type 1 (HIV-1) and 406 men who seroconverted from October 1986 through April 1991. There were 306 deaths. The probabilities of death were compared among men at similar stages of disease who began zidovudine therapy before the diagnosis of AIDS and among those who did not. Relative risks of death were calculated for each of five initial disease stages on the basis of CD4+ cell counts and clinical symptoms and signs appearing over follow-up periods of 6, 12, 18, and 24 months. Adjustments were also made for the use of prophylaxis against Pneumocystis carinii pneumonia (PCP).

Results. After we controlled for CD4+ cell count and symptoms, the use of zidovudine with or without PCP prophylaxis before the development of AIDS significantly reduced mortality in all follow-up periods. The relative risks of death were 0.43 (95 percent confidence interval, 0.23 to 0.78) at 6 months, 0.54 (95 percent confidence interval, 0.38 to 0.78) at 12 months, 0.59 (95 percent confidence interval, 0.44 to 0.79) at 18 months, and 0.67 (95 percent confidence interval, 0.52 to 0.86) at 24 months. After we adjusted for the effects of PCP prophylaxis, zidovudine alone significantly reduced mortality at 6, 12, and 18 months (relative risks, 0.45, 0.59, and 0.70, respectively), but not at 24 months (relative risk, 0.81). Among zidovudine users, those who also used PCP prophylaxis before the development of AIDS had significantly lower mortality at 18 and 24 months than those who did not (relative risks, 0.62 and 0.60, respectively).

Conclusions. The results of this study support the hypothesis that in HIV-1 infection, early treatment with zidovudine and PCP prophylaxis improves survival in addition to slowing the progression to AIDS. (N Engl J Med 1992;326:1037-42.)

THE efficacy of zidovudine in prolonging the survival of patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex was first reported in 1987.1 Subsequent clinical trials examined the efficacy of zidovudine in early human immunodeficiency virus (HIV) infection but used the development of AIDS, rather than death, as the primary outcome measure.2,5 Our own observations in the Multicenter AIDS Cohort Study strongly support the findings that zidovudine slows the progression to AIDS and that prophylaxis against Pneumocystis carinii pneumonia (PCP) also reduces the incidence of PCP among persons taking zidovudine.4

In an observational study of patients with AIDS in Maryland, zidovudine users had a median survival of 690 days, as compared with 280 days for patients who had never used zidovudine.5 In Australia, patients with AIDS who received zidovudine had a median survival of 124 weeks, as compared with 44 weeks for historical controls who never received the drug.4 Although the available experimental1 and observational evidence shows clearly that zidovudine prolongs survival in patients with AIDS, it is not clear whether giving the drug earlier in the course of infection (i.e., before the development of AIDS) prolongs survival in addition to prolonging the time until AIDS develops.2
Cooperative Zidovudine Study have raised doubts about the efficacy of early zidovudine use in prolonging survival. In the Veterans Affairs trial, 338 patients with CD4+ lymphocyte counts of 0.2 to 0.5 cells $\times 10^3$ per liter (200 to 500 per cubic millimeter) were randomly assigned to early zidovudine therapy (at the beginning of the study) or later treatment (when the CD4+ lymphocyte count fell below 0.2 cells $\times 10^3$ per liter). After two years of follow-up, the early-treatment group had significantly fewer AIDS-defining events than the late-treatment group (25 vs. 44, P = 0.02), but no significant differences in numbers of deaths (23 vs. 19). The small numbers of outcomes, the use of high-dose treatment regimens (1500 mg per day), and alterations to the protocol during the study suggest that these mortality data may not reflect the true treatment effect in persons taking zidovudine at currently recommended doses (500 mg per day). Nonetheless, further data are urgently needed to elucidate the effect of early therapy on survival in HIV-infected patients. Several clinical trials, including the Concorde trial of zidovudine in Europe and the continuation of AIDS Clinical Trials Group protocols 019 and 016 in patients with more than 0.5 CD4+ cells $\times 10^3$ per liter, may not provide data from controlled trials to address this issue for several years.

To study this question, we carried out an analysis of mortality in the Multicenter AIDS Cohort Study. The relative risks of death after 6, 12, 18, and 24 months of follow-up were compared in participants who started zidovudine therapy (with or without PCP prophylaxis) before the development of AIDS and in those who did not start to take zidovudine before AIDS developed. These analyses have the advantage of including a large number of outcome events and a large, well-characterized study population representing the spectrum of HIV infection and disease. Since treatment is not randomly assigned in observational prospective studies, selection bias can confound inferences about treatment effects. Care has been taken to minimize potential effects of selection and participation bias.

**Methods**

**Study Population**

The Multicenter AIDS Cohort Study is a prospective study of the natural history of HIV infection among homosexual and bisexual men in the United States. From April 1984 through March 1985, 4954 homosexual and bisexual men were enrolled in four metropolitan areas—Chicago, Pittsburgh, Los Angeles, and the area including Baltimore and Washington, D.C. Men who had been diagnosed with any of AIDS before the time of enrollment or those under 18 years of age were excluded from the study. From April 1987 through December 1990, an additional 587 men were recruited to increase representation from ethnic and racial minority groups; these men were included in the analysis. The study was conducted for semianual follow-up visits, at each of which they completed a study questionnaire, underwent a physical examination, and had blood drawn for hemoglobin, hematocrit, and virologic studies. Details of the study design and methods have been described elsewhere. Of the 4954 men enrolled into the study in 1984 and 1985, 1809 (36.5 percent) were seropositive for HIV type 1 (HIV-1) at entry, and 395 (7.9 percent) who were seronegative at entry became HIV-1-seropositive by April 1991 (i.e., they seroconverted within the first seven years of follow-up). Among the 587 later recruits, 355 (60.1 percent) were seropositive at entry, and 13 (2.2 percent) seroconverted by April 1991. HIV-1 seropositivity was determined by enzyme-linked immunosorbent assay and confirmed with Western blot testing. This analysis included all men seropositive for HIV at entry and those who seroconverted before the time of the visit used as a base line in this study and who had not contracted AIDS or died by the time of their sixth study visit (visit 6).

The analysis was restricted to the period beginning with study visit 6 (October 1986 through March 1987). This period was chosen because previously zidovudine was unavailable, and no participants in the study reported its use until visit 6. In addition, the selection of this starting time for the study minimized the effect of any secular trends in survival time in the patients not taking zidovudine. Deaths and diagnoses of AIDS from October 1, 1986, through April 1, 1991, were included in the study.

**Stage of Disease and Risk of Death**

To examine the effect on survival of zidovudine (with or PCP prophylaxis) and treatment before the onset of AIDS, mortality rates were calculated for patients who entered the study period in one of five starting disease states and were followed for periods of 6, 12, 18, and 24 months. For each participant a separate starting disease state was defined for each study visit, beginning with visit 6 (October 1986 through March 1987). The five disease states, as defined by CD4+ lymphocyte counts and clinical symptoms and signs, were as follows: state 1, >350 CD4+ cells $\times 10^3$ per liter (450 cubic millimeter); state 2, 0.2 to 349 CD4+ cells $\times 10^3$ per liter (200 to 349 cubic millimeter) and asymptomatic; state 3, 0.2 to 349 CD4+ lymphocytes $\times 10^3$ per liter and asymptomatic; state 4, <0.2 CD4+ cells $\times 10^3$ per liter and asymptomatic. Symptomatic status was defined by the presence during the previous six months of one or more of the following clinical symptoms or signs: fever (temperature, >37.5°C) or >2 weeks, oral candidiasis, diarrhea for >2 weeks, weight loss of >4.5 kg (10 lb), or oral hairy leukoplakia, or herpes zoster. Since treatment before the diagnosis of AIDS during the follow-up period was the independent variable of primary interest, AIDS could not be present at base line. Death was the primary outcome. The rates of death at 6, 12, 18, and 24 months were then calculated separately for men who started treatment before their diagnosis of AIDS and for those who did not.

The use of zidovudine was defined as any such use reported a having occurred before the time of a first AIDS-defining illness. The comparison group either did not take zidovudine at any time or delayed the start of treatment until after a first AIDS-defining illness. Data were also collected on the concurrent use of drugs prevent first episodes of PCP. PCP prophylaxis was defined as the reported use of trimethoprim–sulfamethoxazole, aerosolized pentamidine, trimethoprim–dapsone, or dapsone alone at any time before a first AIDS-defining illness.

**Outcomes and Follow-up**

We report analyses in which mortality from all causes was used as the outcome variable. There were 306 deaths during the study period (October 1, 1986, through April 1, 1991). Analysis were all conducted with only HIV-related deaths used as the outcome variable, but these yielded essentially the same results. Causes of death were obtained from death certificates, autopsy reports, and review of medical records. Causes of death were available for 96 percent of all deaths reported through April 1, 1991.

In the cohort recruited in 1984 and 1985, follow-up data as of April 1, 1991, were available for 91 percent of the men who seroconverted and 90 percent of those who had been seropositive. During the period of the study (October 1, 1986, through April 1, 1991), the use of follow-up did not differ substantially between the group who used zidovudine before the onset of AIDS (3 percent) and the group that did not (5 percent).

**Log-Linear Models**

A log-linear regression model was used to estimate the effect on survival. The model assumes that the risk of death during any follow-up period is a function of the disease state at
beginning of the period, the use of zidovudine before the development of AIDS, and the use of PCP prophylaxis before the development of AIDS. Interactions of zidovudine with the starting disease state were included in the model to examine whether the effectiveness of zidovudine varied according to the stage of the disease when the treatment was begun. Because insufficient numbers of men used PCP prophylaxis during early disease to permit analysis of the effect of the stage of disease, only a main effect was included in all models. The timing of the base-line study visit was included to test for secular trends in rates of disease progression. To determine whether the use of PCP prophylaxis before the onset of AIDS independently reduced mortality in addition to the effects of zidovudine, the risk of mortality was compared between men who used such PCP prophylaxis before the development of AIDS and men who used only zidovudine. In this subgroup analysis, the risk of death was assumed to depend on the starting disease state and on the use of PCP prophylaxis before the development of AIDS. Because of small numbers, only three disease-state categories were used: >0.35, 0.2 to 0.349, and <0.2 CD4+ cells ×10^6 per liter.

In this analysis, the follow-up periods for each participant could overlap when the observation period exceeded six months. Such repeated observations were likely to be correlated. This correlation was taken into account when standard errors and confidence intervals were estimated from the statistical model.¹¹

**Validation of Zidovudine Reporting**

As we have reported earlier,¹² the questionnaire about zidovudine use was validated in relation to the values for mean corpuscular volume that were ascertained at the respective study visits. The degree of validity of the questionnaire was high, with results for sensitivity and specificity very close to those reported in AIDS Clinical Trials Group protocol 019.³

**RESULTS**

**Overall Mortality Rates**

The probabilities of death according to starting disease state and follow-up period were calculated by dividing the total number of deaths in each stratum by the total number of observations in that stratum. These data are presented in Table 1. Mortality increased predictably with more advanced disease and increasing duration of follow-up. Mortality rates remained low for men who entered the follow-up period with >0.35 CD4+ cells ×10^6 per liter (Table 1 and Fig. 1). Thus, the mortality rate in this group was not high enough to allow the precise estimation of differential mortality between the two treatment groups of primary interest (zidovudine therapy before the development of AIDS and no such therapy before that time), and confidence intervals remained wide in this stratum (Table 2). However, there were substantially more deaths among men beginning with CD4+ cell counts below 0.35×10^6 per liter, allowing a more powerful assessment of early treatment within these strata (Table 1).

**Effect of Early Zidovudine Use on Mortality**

Mortality rates in the two study groups are presented in Figure 1 according to starting disease state, and relative risks of death associated with early treatment are shown in Table 2. After six months of follow-up, early treatment was associated with a reduced risk of dying for men in disease states 3, 4, and 5 at the start of the study. The protective trend was statistically significant for men starting with fewer than 0.2 CD4+ cells ×10^6 per liter and no symptoms (state 4), but wide confidence intervals were found for men starting in states 3 and 5. The effect of treatment did not vary significantly according to starting state, so a pooled relative risk was calculated as a summary statistic of the overall association of treatment with death. At six months of follow-up, after adjustment for the starting state, the use of zidovudine (with or without PCP prophylaxis) before the development of AIDS was significantly associated with a reduced risk of mortality (relative risk, 0.43; 95 percent confidence interval, 0.23 to 0.78). After adjustment for the effects of PCP prophylaxis, zidovudine use alone remained independently associated with reduced mortality (relative risk, 0.45; 95 percent confidence interval, 0.21 to 0.98) after six months of follow-up.

After 12, 18, and 24 months of follow-up, there were trends toward lower mortality with early treatment in all groups. These trends reached statistical significance for men in starting state 4 after 12 months, for those in states 3 and 4 after 18 months, and for those in states 2 and 4 after 24 months. The overall effects of treatment before the development of AIDS were significant at all three follow-up periods: the pooled relative risks of death were 0.54 after 12 months (95 percent confidence interval, 0.38 to 0.78), 0.59 after 18 months (95 percent confidence interval, 0.44 to 0.79), and 0.67 after 24 months (95 percent confidence interval, 0.52 to 0.86) (Fig. 2). Zidovudine use alone remained independently associated with a reduction in mortality, after adjustment for the effects of PCP prophylaxis, at 12 months (relative risk, 0.59; 95 percent confidence interval, 0.38 to 0.91) and 18 months (relative risk, 0.70; 95 percent confidence interval, 0.50 to 0.99), but not at 24 months (relative risk, 0.81; 95 percent confidence interval, 0.61 to 1.08).

Patterns of zidovudine use varied according to the length of follow-up. The mean proportion of time in which the zidovudine users actually took the drug during the follow-up periods was 75 percent, 60 per-

Table 1. Overall Rates of Death, According to Duration of Follow-up and Starting Disease State.

<table>
<thead>
<tr>
<th>STARTING STATE</th>
<th>6 MO</th>
<th>12 MO</th>
<th>18 MO</th>
<th>24 MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 COUNT</td>
<td>SYMPTOMS</td>
<td>NO. OF VISITS</td>
<td>% OF MEN WHO DIED</td>
<td></td>
</tr>
<tr>
<td>&gt;0.35</td>
<td>Not applicable</td>
<td>6127</td>
<td>0.16</td>
<td>5001</td>
</tr>
<tr>
<td>0.2-0.349</td>
<td>No</td>
<td>1484</td>
<td>0.20</td>
<td>1218</td>
</tr>
<tr>
<td>0.2-0.349</td>
<td>Yes</td>
<td>435</td>
<td>0.92</td>
<td>367</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>No</td>
<td>752</td>
<td>1.86</td>
<td>621</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>Yes</td>
<td>493</td>
<td>4.06</td>
<td>387</td>
</tr>
<tr>
<td>All participants</td>
<td>9291</td>
<td>0.55</td>
<td>7594</td>
<td>1.96</td>
</tr>
</tbody>
</table>

*The numbers shown are the numbers of study visits. The same patient could contribute more than one such visit to the analysis.

**Participants in this stratum were not subdivided according to symptomatic or asymptomatic status.**
cent, 53 percent, and 46 percent of the periods lasting 6, 12, 18, and 24 months, respectively.

**Effect of Early PCP Prophylaxis on Mortality**

To separate the effects on mortality of zidovudine use before the development of AIDS and of PCP prophylaxis, relative risks were estimated from log-linear models in which we adjusted for independent effects of each treatment variable. In these models, after adjustment for zidovudine use, PCP prophylaxis was associated with a trend toward lower mortality at 6, 12, and 18 months (relative risk, 0.45, 0.59, and 0.70, respectively), but this trend reached statistical significance only after 24 months of follow-up (relative risk, 0.64; 95 percent confidence interval, 0.43 to 0.95). As we have reported previously, 4,12 relatively few participants in the Multicenter AIDS Cohort Study used PCP prophylaxis during this period (1986 through 1991), and they almost always used it in conjunction with zidovudine. Therefore, to assess whether PCP prophylaxis offered any protection in addition to that afforded by zidovudine, we conducted subanalyses in which only those men who used zidovudine before the development of AIDS were included. In this group the risk of mortality was compared between men who also used primary PCP prophylaxis (i.e., that preceding a diagnosis of AIDS) and those who did not (Table 3). No consistent reduction in mortality associated with the use of primary PCP prophylaxis was seen in participants starting with 200 CD4+ cells per liter. For those with CD4+ cell counts below this level, however, protective trends were seen at 6, 12, 18, and 24 months. To determine whether primary PCP prophylaxis reduced overall mortality, pooled relative risks and confidence intervals were calculated from the log-linear models for each follow-up period (Table 3). These estimates were adjusted to reflect the changing disease state. Protective trends were again seen at 6 and 12 months, and they reached statistical significance at 18 and 24 months (Table 3).

**DISCUSSION**

In a previous study, we showed that early zidovudine use and primary PCP prophylaxis were both associated with a slowing in the progression of HIV-1 infection to AIDS in a large observational cohort of homosexual and bisexual men. 4 Clinical trials had also shown that zidovudine was efficacious in slowing this progression,2,3 but data from such trials that addressed the efficacy of primary PCP prophylaxis given early in the course of HIV-1 infection were not available until 1991. 13 In both a clinical trial and observational studies, 5, 6 zidovudine has been shown to increase survival in patients with AIDS. However, a recent clinical trial of zidovudine therapy starting before as compared to after disease diagnosis showed no survival benefit. 12 In these trials, patients were followed for only a short period of time, and many had AIDS when they were randomized to treatment. 4 In contrast, the MCC cohort is largely comprised of asymptomatic men, and therefore the study participants are more likely to be followed for years without AIDS or PCP. The fact that we observed a trend toward lower mortality in those who used primary prophylaxis is consistent with previous findings. 4, 12 However, the difference was not statistically significant, and we need to be cautious in interpreting these results. The cohort includes men who had a median CD4+ cell count of 520 cells per liter, and thus many men entered the study with a reduced immune system. The results are therefore less likely to be due to the slowing of progression of disease, and more likely to be due to a trial effect. In conclusion, early zidovudine use and primary PCP prophylaxis were associated with a trend toward lower mortality in this cohort. Future studies should focus on understanding the mechanisms by which these interventions reduce mortality.
pared with after either the development of AIDS or CD+ cell counts < 0.2 × 10^6 per liter showed no survival advantage for the early-treatment group, despite a slowing of the progression to AIDS. There are also now adequate data from observational studies and clinical trials to show that PCP prophylaxis (starting either before or after an AIDS diagnosis) reduces the incidence of PCP during HIV-1 infection, but it is still not clear that such prophylaxis reduces mortality. To determine whether early treatment alters the natural history of progression of HIV-1 infection to death, we used observational methods to study the effectiveness of treatment in a community-based cohort. The relative risks of death were compared between subjects who started treatment with zidovudine (with or without PCP prophylaxis) before the development of AIDS and those who did not. To minimize the effects of a bias related to selection or participation, we stratified the analyses according to the starting disease state on the basis of CD4+ cell counts and HIV-related symptoms and signs. Since sicker patients are more likely to receive zidovudine, this bias tends to be conservative; that is, to minimize treatment effects. In addition, the overall effects of early use of zidovudine and PCP prophylaxis were calculated from log-linear models that were adjusted for starting disease state and that accounted for the multiple observations available for each participant (i.e., one for each study visit since October 1986).

Early treatment was found to be associated with significantly reduced mortality at 6, 12, 18, and 24 months (Fig. 2). In general, men starting with 0.2 to 0.549 CD4+ cells × 10^6 per liter appeared to benefit most from treatment. This finding is consistent with that from our earlier study, but the differential effect of treatment between strata did not reach statistical significance in either study. The confidence intervals were wide for participants starting with CD4+ cell counts ≥ 0.35 × 10^6 per liter. Since very few outcomes were seen in this group, a longer follow-up period will be needed before we can confidently exclude a significant therapeutic effect in this group. Zidovudine use was independently associated with reduced mortality at 6, 12, and 18 months, but not at 24 months. Further studies are needed to determine whether this finding represents a diminution of the therapeutic effect of zidovudine over time or whether it merely reflects the fact that zidovudine users took the drug for only 46 percent of this longer period.

PCP prophylaxis was more clearly protective after 18 and 24 months than after shorter follow-up periods. This may reflect its specificity of action. Since it has no antiviral effect, it can reduce overall mortality only by reducing mortality from PCP. This relation is likely to be more difficult to discern over shorter periods, in which there are fewer outcome events. The prevention of PCP is likely to shift the cause of death from PCP to opportunistic infections that occur later in the course of infection (e.g., Mycobacterium avium complex), thus lengthening overall survival.

Observational studies of the effectiveness of treatment are potentially subject to bias. As we have previously discussed, such bias tends to be conservative (i.e., likely to underestimate the true effect of treatment), since patients who receive treatment tend to be somewhat sicker than those who do not. In HIV infection, the CD4+ cell count and clinical symptoms determine who will receive antiviral therapy, as well as who is likely to have progression of disease. Therefore, stratification according to starting disease state and estimation of risk adjusted according to starting state reduce the biases in selection and partic-

Table 3. Rates of Death among Men Taking Zidovudine, According to Use or Nonuse of PCP Prophylaxis before a Diagnosis of AIDS.

<table>
<thead>
<tr>
<th>DURATION OF FOLLOW-UP</th>
<th>STARTING STATE NO.</th>
<th>PCP PROPHYLAXIS†</th>
<th>RELATIVE RISK (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>6 mo</td>
<td>1</td>
<td>165 (0.00)</td>
<td>615 (0.00)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>250 (0.00)</td>
<td>390 (0.51)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>388 (1.55)</td>
<td>344 (2.33)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>803 (0.53)</td>
<td>1349 (0.94)</td>
</tr>
<tr>
<td>12 mo</td>
<td>1</td>
<td>191 (0.52)</td>
<td>635 (0.16)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>292 (0.34)</td>
<td>385 (1.04)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>350 (7.43)</td>
<td>276 (10.14)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>833 (2.49)</td>
<td>1296 (3.37)</td>
</tr>
<tr>
<td>18 mo</td>
<td>1</td>
<td>230 (0.87)</td>
<td>644 (0.62)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>282 (3.19)</td>
<td>302 (2.96)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>389 (11.76)</td>
<td>224 (22.32)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>811 (4.39)</td>
<td>1170 (6.97)</td>
</tr>
<tr>
<td>24 mo</td>
<td>1</td>
<td>266 (2.26)</td>
<td>586 (1.19)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>263 (5.32)</td>
<td>254 (6.69)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>213 (18.78)</td>
<td>185 (38.38)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>742 (6.88)</td>
<td>1025 (11.18)</td>
</tr>
</tbody>
</table>

*See Table 1 or the Methods section for definitions of the starting states. Rates shown for "all" are adjusted for starting state by the direct method.
†The numbers shown are the numbers of study visits. The same patient could contribute more than one such visit to the analysis. Increased numbers of patients in the groups with longer follow-up are due to the inclusion of patients for whom earlier values were missing.
‡The relative risks of death shown for each stratum are crude ratios of the reported rates. Overall relative risks were estimated from a log-linear model, with adjustment for starting state and accounting for the correlation of values for multiple observations of a given patient, permitting the calculation of confidence intervals.
ipation that can be anticipated in cohort studies.\textsuperscript{4} In a previous study, therapy reduced the risk of progression to AIDS by 49 percent at 12 months,\textsuperscript{4} a figure that is comparable to the magnitude of benefit measured in clinical trials.\textsuperscript{2,3}

Another potential source of bias is the differential follow-up of treated and untreated persons. In the Multicenter AIDS Cohort Study, complete follow-up data were available for 91 percent of the men who seroconverted and 90 percent of those who were already seropositive when they were recruited in 1984 and 1985. This analysis was restricted to the time of their sixth visit and thereafter, when the loss to follow-up was only 3 percent among men using zidovudine before the development of AIDS, as compared with 5 percent in the group that did not use zidovudine before that point. This difference is not significant, but if it had any effect, it would be to underestimate the effectiveness of treatment slightly if the proportion of deaths was either the same in each group or higher in the untreated group (the most likely possibilities).

Finally, zidovudine use was validated in relation to values for mean corpuscular volume obtained at the time the medication questionnaire was completed. As has been outlined previously, the reporting of zidovudine use had a high level of validity and compared favorably in this respect with data from clinical trials.\textsuperscript{3,4,12}

In conclusion, we found that the initiation of treatment with zidovudine (with or without PCP prophylaxis) before the development of AIDS was significantly associated with a reduced risk of mortality after 6, 12, 18, and 24 months of follow-up. The use of zidovudine alone was independently associated with reduced mortality after 6, 12, and 18 months, as was the use of PCP prophylaxis after 18 and 24 months. These data suggest that both antiviral and anti-PCP prophylaxis are necessary to maximize the survival benefit. The additional survival time attributable to these drugs and to newer treatments, such as didanosine and dideoxycytidine, and prophylaxis against opportunistic infections other than PCP, should be the focus of ongoing investigation in observational studies,\textsuperscript{18} in addition to experimental investigation in therapeutic clinical trials.

We are indebted to Dr. Donald Hoover for helpful discussions on methods and to Ms. Harriet Grossman for assistance in the preparation of the manuscript.

**REFERENCES**