Zidovudine in Persons with Asymptomatic HIV Infection and CD4+ Cell Counts Greater than 400 per Cubic Millimeter

David A. Cooper, Jose M. Gatell, Susanne Kroon, Nathan Clumeck, Judith Millard, Frank-D Goebel, Johan N. Bruun, Georg Stingl, Rex L. Melville, Juan Gonzalez-Lahoz, John W. Stevens, A. Paul Fiddian, for The European-Australian Collaborative Group

ABSTRACT

Background Zidovudine therapy is of benefit in the treatment of symptomatic and asymptomatic human immunodeficiency virus (HIV) infection in persons with CD4+ cell counts of less than 500 per cubic millimeter. The efficacy, safety, and duration of benefit of zidovudine in those with 500 or more CD4+ cells per cubic millimeter are uncertain.

Methods In a double-blind, placebo-controlled trial, 993 patients with asymptomatic HIV infection and CD4+ cell counts above 400 per cubic millimeter were randomly assigned to receive zidovudine (500 mg twice daily) or placebo for three years. The primary end point was progression of disease, as defined by the development of Centers for Disease Control and Prevention (CDC) group IV disease (including recurrent oral candidiasis, hairy leukoplakia, or progressive diarrhea) or two CD4+ cell counts below 350 per cubic millimeter. This outcome measure was changed from the original end point of the acquired immunodeficiency syndrome (AIDS) or advanced AIDS-related complex to reflect changes in recommendations for management. The study was terminated after the first interim analysis.

Results Disease progression was significantly less frequent in the zidovudine group (relative risk, 0.56; 95 percent confidence interval, 0.43 to 0.75; P<0.001 by the log-rank test). The probability of disease progression at two years was 0.19 with zidovudine, as compared with 0.34 with placebo (95 percent confidence interval for the difference, -0.21 to -0.08). Progression to CDC group IV disease was reduced by half in the zidovudine recipients (relative risk, 0.49; P = 0.049) and decline in CD4+ cell counts to below 350 per cubic millimeter was reduced by 40 percent (relative risk, 0.60; P<0.001). The inclusion of early HIV disease events (oral candidiasis, oral hairy leukoplakia, and herpes zoster) as end points confirmed the effects of zidovudine on the progression of clinical disease (relative risk, 0.55; 95 percent confidence interval, 0.37 to 0.84; P = 0.004). The median duration of treatment was 94 weeks. Severe hematologic or clinical side effects were rare.

Conclusions Treatment with zidovudine benefits HIV-infected persons with CD4+ cell counts above 400 per cubic millimeter. Despite the use of doses larger than those now generally prescribed, zidovudine was well tolerated for up to three years by most of our patients.

When our European-Australian Collaborative Group study was initiated, zidovudine had been shown to provide clinical benefit in patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex, including reductions in mortality and in the frequency of

opportunistic infections[1]. While our study was under way, two other major placebo-controlled trials reported by the AIDS Clinical Trials Group demonstrated that treatment with zidovudine delayed disease progression in early symptomatic and asymptomatic patients with fewer than 500 CD4+ cells per cubic millimeter[2,3]. Although a total daily dose of 1500 mg was used in the original study,[1] the results of several trials[3,4,5] have subsequently indicated that lower daily doses, between 500 and 600 mg, are equally effective for most patients.

Since all the major placebo-controlled trials of zidovudine have been terminated early after interim analyses, long-term data on efficacy and safety have been available only from population studies[6,7,8,9] or trials of dose ranges[4,5]. The Veterans Affairs study suggested that delayed zidovudine therapy resulted in more progression of disease than early intervention[10]. Differing opinions persist about the duration of benefit after intervention at different stages of human immunodeficiency virus (HIV) infection, and therefore about the optimal time to initiate treatment[11,12,13]. We report the results of a three-year study designed to determine the efficacy and safety of zidovudine in reducing disease progression in patients with early asymptomatic HIV infection and CD4+ cell counts above 400 per cubic millimeter. The trial was terminated in January 1992 after the first interim analysis.

Methods

Patient Population

Patients at least 18 years old with asymptomatic HIV infection or persistent generalized lymphadenopathy were eligible for enrollment if they met the following criteria: a documented history of HIV-antibody seropositivity (i.e., at least two confirmed positive tests, one within three months of enrollment) and a CD4+ cell count above 400 cells per cubic millimeter within four weeks before entry. All patients gave written informed consent before participation in the study. Subjects were recruited from 56 centers in Australia, Austria, Belgium, Denmark, Finland, Germany, Iceland, Luxembourg, Norway, and Spain. Approval from the ethics committee at each center was obtained before the start of the study.

Study Design

The study was designed as a randomized, placebo-controlled parallel-group trial. At enrollment, the patients were randomized according to a permuted-blocks scheme, stratified according to center, in which the block size was six patients. When the study began in 1988, the primary clinical end point was the development of AIDS or severe AIDS-related complex. In 1989, after the preliminary reports of the two studies by the AIDS Clinical Trials Group, the International Coordinating Committee recognized that it had become unacceptable not to offer open-label treatment with zidovudine to persons whose CD4+ cell counts had fallen below 200 per cubic millimeter, even if they remained asymptomatic. Accordingly, patients were allowed optional withdrawal from the study if their CD4+ counts were less than or equal to 200 cells per cubic millimeter. Then, during 1990, the results of these studies were published,[2,3] leading to an extension of the licensed indications for zidovudine and to further changes in medical practice. Although medical practice differed in some participating countries, a consensus was reached that persons with disease that met the criteria for group IV of the Centers for Disease Control and Prevention (CDC) system or whose CD4+ cell counts dropped below 350 per cubic millimeter should also be offered zidovudine therapy. Hence, the final primary end point became the development of CDC group IV disease or the determination of two CD4+ cell counts below 350 per cubic millimeter on separate occasions at least one month apart, whichever occurred first. All changes in the study design and end

points were made and formalized by the International Coordinating Committee without awareness of the assigned treatments.

Treatment Regimen, Evaluation of Patients, and Follow-up

Patients were randomly assigned to receive two 250-mg capsules of zidovudine or matching placebo by mouth every 12 hours for up to three years. Side effects were managed according to guidelines prepared before the start of the study. Dose reduction to 250 mg every 12 hours or the permanent discontinuation of therapy was recommended when there was evidence of progressive bone marrow suppression or any other adverse reaction deemed sufficiently serious. The use of other drugs thought to have antiretroviral activity and the use of immunomodulatory agents were prohibited.

After enrollment and base-line laboratory evaluation, patients were assessed every 4 weeks until week 24 and every 12 weeks thereafter. When possible, patients who were no longer receiving the study medication were followed every 12 weeks and assessed according to the protocol. Routine blood samples were monitored. Serum HIV p24 antigen levels and CD4+ cell counts were determined every 4 weeks until week 12 and every 12 weeks thereafter. Data on variables that might have led to unblinding (mean corpuscular volume and p24 antigen levels) were handled by staff members not involved with patient care or monitoring of the study.

Assessment of End Points

All definitions of study end points were formalized before the termination of the study. Data on each end point were reviewed by an End Points Committee. The investigators were asked to clarify end points when resolution of questionable diagnoses was required. End points were reviewed on an ongoing basis throughout the study, with all evaluations made by the End Points Committee carried out with the committee members unaware of the assigned treatments.

Data were reviewed retrospectively in order to include end points of less advanced HIV disease and immunologic end points that had occurred before the changes to the end points were implemented. All information necessary for the newly defined end points had already been collected prospectively on the case-record forms. In the analyses, data on the end points were censored at the point of disease progression.

For the purposes of this trial and in an attempt to standardize reporting across countries, modified but strict criteria for the conditions in CDC group IV-C2 were used. During the initial reviews of blinded data, the End Points Committee observed many reported secondary infections that were rejected as indicative of CDC group IV disease because of the strict criteria. The committee was, however, able to define an end point of clinical HIV disease that included early events of HIV disease as well as group IV events, whichever occurred first.

There were four separate end points as defined by the End Points Committee. First, AIDS was defined on the basis of CDC criteria available at the start of the trial[14]. The protocol also specified, however, that peripheral neuropathy should be regarded as an AIDS-defining event. Severe AIDS-related complex was defined as unexplained weight loss of ≥7 kg or at least 10 percent of body weight, unexplained oral candidiasis, or both, along with at least one of the following: progressive diarrhea for more than one month, fever (temperature >38 °C) persisting for more than one month without infectious cause, oral hairy leukoplakia, multidermatomal herpes zoster, and pulmonary tuberculosis. Second, modified criteria for

conditions assigned to CDC group IV-C2 were used, as follows: oral candidiasis had to be documented on consecutive occasions at least three months apart, described at least once as moderate or severe and requiring topical therapy or at least once requiring systemic therapy; oral hairy leukoplakia had to be reported on consecutive occasions at least three months apart with a severity described as moderate or severe at least once or at least once requiring treatment with acyclovir; and herpes zoster had to be described as a widespread dissemination of rash involving nonadjacent dermatomes. Two patients with progressive diarrhea determined by the End Points Committee to have CDC group IV disease were analyzed as having CDC group IV-C2 disease. The analysis of progression to CDC group IV disease included patients with AIDS, severe AIDS-related complex, and CDC group IV-C2 disease. Third, the criteria for early clinical HIV disease were as follows: recurrent or persistent oral candidiasis or oral hairy leukoplakia when the occurrences were observed by the investigator, were documented by assessments at least 12 weeks apart, were otherwise unexplained, and did not fulfill our criteria for inclusion in CDC group IV-C2. In addition, localized herpes zoster infections were included in the analysis of early HIV disease. Analyses of progression to clinical HIV disease included patients with AIDS or severe AIDS-related complex, those in CDC group IV-C2, and those with early HIV disease. Fourth, the CD4+ end point was defined as the first time a patient's CD4+ cell count fell below 350 cells per cubic millimeter, provided that there was a subsequent and consecutive count also below 350 cells per cubic millimeter at least 28 days later.

Data Management and Statistical Analysis

Data from the participating centers were verified against selected source documents, including the patients' records of eligibility. Data were routinely dual-entered for verification and checked for anomalies and outliers.

Variables related to the time to a critical event were analyzed by survival methods, including Kaplan-Meier estimates, log-rank tests, and determinations of relative risk. These variables were analyzed on an intention-to-treat basis. However, as specified in the study design, data were censored three months after the termination of blinded treatment with the study medication. The statistical significance of the primary objective was compared against a nominal significance level of 0.022, corresponding to an overall significance level of 0.05 with allowance for two interim analyses. Other variables of interest were summarized with descriptive statistics, such as medians, tables, and 95 percent confidence intervals for treatment effects.

The size of the study sample was recalculated in March 1991 after the amendment to the protocol that allowed the optional withdrawal of patients who had either a reduction in CD4+ cell count to less than 350 per cubic millimeter or progression to CDC group IV disease. The size of the revised sample was based on the objective of detecting a reduction from 20 percent to 10 percent in disease progression under the revised definition with use of the log-rank test with 90 percent power at the 0.05 significance level. An adjustment was made to allow for the interim analyses and for patient withdrawals. The calculations indicated that 836 patients would be required to show a treatment effect on disease progression as redefined above.

Results

Patient Population

A total of 993 patients were enrolled in the trial between December 1988 and January 1992. The study was terminated in January 1992, when interim analysis showed a difference in overall disease progression that was significant at the P = 0.001 level. Of the 993 patients recruited, 9 were not included in the analyses of safety and efficacy because no follow-up information was available. A further eight patients were considered to have CDC group IV disease at entry and were therefore excluded from all analyses except those of safety. In addition, one patient was randomized twice by error.

Of the 984 eligible patients, 489 were assigned to placebo and 495 to zidovudine. The demographic and clinical characteristics of the treatment groups were similar at entry (Table 1). Median CD4+ cell counts at entry were similar in both groups (Table 1). The prevalence of positivity for HIV p24 antigen at entry was 11 percent in the placebo group and 9 percent in the zidovudine group. Other key clinical and laboratory measures were evenly matched between the two treatment groups. At the time of study termination, the median duration of treatment was 93 weeks for those assigned to placebo and 94 weeks for those assigned to zidovudine. Three hundred eight patients withdrew from blinded treatment during the study (Table 2).

Table 2

CHARACTERISTIC	PLACEBO (N = 489)	ZIDOVUDINE (N = 495)
Age (yr)*	31	31
Male sex (%)	83	88
White race (%)	96	96
Risk factor (%)		
Homosexual or bisexual sex	66	68
Injection-drug use	16	17
Heterosexual sex	14	12
Use of blood products	2	1
Other	1	2
CDC group II disease (%)	54	58
Hemoglobin (g/dl)*	14.9	15.0
Neutrophils (per mm^3)*	3100	3200
CD4+ count (per mm^3)†		
Median	591	595
Mean ±SD	651±220	650±230
Stratum (% of group)		
<400	5	5
400–499	24	20
500–749	44	48
>750	26	25

*Median values are given.

†The values for CD4+ cell counts were the average of all counts determined within the six weeks before entry and at base line. For 11 patients, 7 in the placebo group and 4 in the zidovudine group, these base-line data were not available.

Table 2

VARIABLE	STUDY GROUP		ALL PATIENTS
	PLACEBO	ZIDOVUDINE	
No. of patients	489	495	984
Median weeks of follow-up*	93	94	93
	no. of patients		
Eligible but never started treatment	4	4	8
Withdrew from treatment	135	173	308
Adverse experience	10	27	37
Deviation from protocol	7	8	15
Withdrew consent	79	93	172
Lost to follow-up after starting treatment	37	42	79
Other (e.g., pregnancy)	2	3	5

*Measured from randomization to January 31, 1992.

Progress
ion of Disease

Overall disease progression as defined in the protocol (progression to AIDS or severe AIDS-related complex, CDC group IV-C2 disease, or two CD4+ cell counts below 350 per cubic millimeter) developed in 129 patients in the placebo group, as compared with 76 patients in the zidovudine group (relative risk, 0.56; 95 percent confidence interval, 0.43 to 0.75; $P<0.001$ by the log-rank test) (Figure 1). The number of patients whose disease progressed is shown according to base-line CD4+ cell count in Table 3, along with the overall risk ratio. The Kaplan-Meier probability of disease progression at two years was 0.34 in the placebo group and 0.19 in the zidovudine group (95 percent confidence interval for the difference, -0.21 to -0.08) (Figure 1).

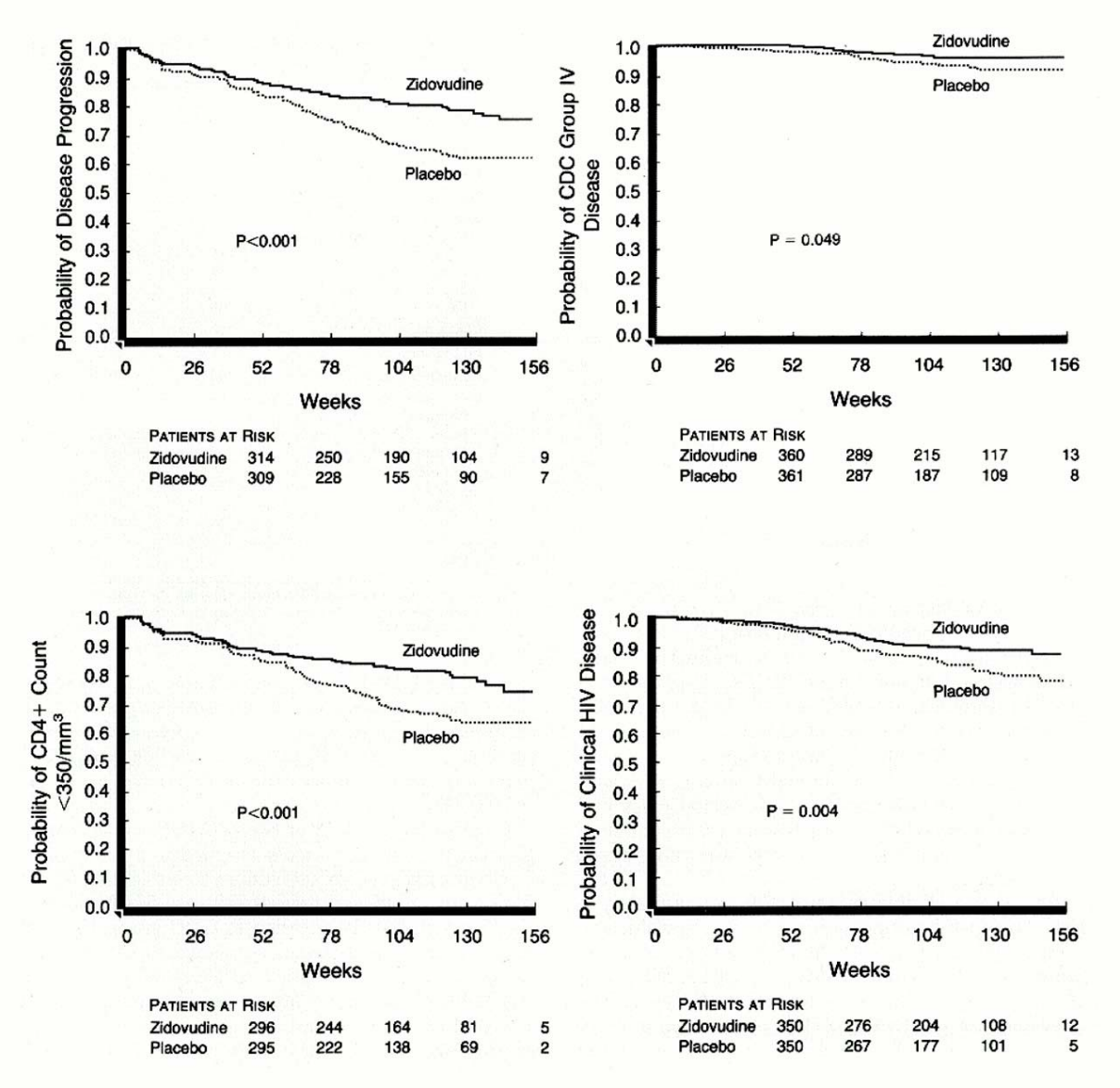

Figure 1. Kaplan-Meier Estimates of Time to Study End Points in the Patients Assigned to Zidovudine and Placebo.

The curves show the time to progression of disease as defined in the protocol, to CDC group IV disease, to a CD4+ cell count of less than 350 per cubic millimeter, and to clinical HIV disease.

Table 3

End Point	Base-Line CD4+ Cells per Cubic Millimeter			Overall*		Risk Ratio (95% Confidence Interval)
	400–499	500–749	>750			
	number (percent)					
Disease progression						
Zidovudine	24 (25)	37 (16)	6 (5)	76	(16)	0.56 (0.43–0.75)
Placebo	58 (53)	52 (25)	12 (10)	129	(28)	
AIDS or severe AIDS-related complex						
Zidovudine	1 (1)	5 (2)	0	6	(1)	0.59 (0.21–1.61)
Placebo	1 (1)	6 (3)	3 (2)	10	(2)	
CDC group IV disease						
Zidovudine	2 (2)	8 (3)	1 (1)	11	(2)	0.49 (0.24–1.01)
Placebo	5 (4)	14 (7)	3 (2)	22	(5)	
Clinical HIV disease						
Zidovudine	6 (6)	21 (9)	4 (3)	35†	(7)	0.55 (0.37–0.84)
Placebo	19 (17)	32 (15)	8 (6)	62	(13)	
CD4+ count $<350/mm^3$						
Zidovudine	23 (24)	33 (14)	5 (4)	70	(15)	0.60 (0.44–0.81)
Placebo	55 (50)	42 (20)	9 (7)	113	(25)	

*Includes all end points regardless of base-line CD4+ cell count and therefore includes a group of subjects with base-line CD4+ cell counts of less than 400 per cubic millimeter. In the analyses of AIDS or severe AIDS-related complex, CDC group IV disease, and clinical HIV disease, the percentages shown were calculated on the basis of the denominators used in the analysis of safety. Patients with CD4+ counts below 350 per cubic millimeter at entry and those with missing data on CD4+ counts at entry were excluded from the analyses of disease progression and CD4+ count of less than 350 per cubic millimeter.

†Includes one event in the zidovudine group in a patient for whom base-line data on CD4+ cell counts were missing.

Progression to AIDS or severe AIDS-related complex occurred in 10 patients assigned to placebo and 6 patients assigned to zidovudine (relative risk, 0.59; 95 percent confidence interval, 0.21 to 1.61; P = 0.29) (Table 3 and Table 4). Progression to CDC group IV disease occurred in 22 patients assigned to placebo, as compared with 11 assigned to zidovudine (relative risk, 0.49; 95 percent confidence interval, 0.24 to 1.01; P = 0.049) (Table 3 and Table 4, Figure 1). The probability of progression to CDC group IV disease at two years was 0.06 in the placebo group, as compared with 0.03 in the zidovudine group (95 percent confidence interval for the difference, -0.06 to -0.01). Progression to a CD4+ cell count below 350 per cubic millimeter occurred in 113 recipients of placebo, as compared with 70 recipients of zidovudine (relative risk, 0.60; 95 percent confidence interval, 0.44 to 0.81; P<0.001) (Table 3 and Figure 1). The probability of progression to a CD4+ cell count of less than 350 per cubic millimeter at two years was 0.32 in the placebo group, as compared with 0.17 in the zidovudine group (95 percent confidence interval for the difference, -0.21 to -0.07). Zidovudine significantly reduced the overall progression of disease as defined in the study, as well as delaying the onset of CDC group IV disease and the decline of CD4+ cell counts to below 350 per cubic millimeter.

Table 4

	Placebo	Zidovudine
	no. of patients	
AIDS or severe AIDS-related complex		
Pneumocystis carinii pneumonia	4	0
Peripheral neuropathy	0	1
Kaposi's sarcoma	3	2
Cryptosporidiosis	0	1
Toxoplasmosis	1	0
Progressive multifocal leukoencephalopathy	0	1
Leishmaniasis	0	1
Extrapulmonary tuberculosis	1	0
Oral candidiasis/oral hairy leukoplakia	1	0
Total	10	6
CDC group IV (1st event)		
AIDS	9	6
Oral hairy leukoplakia	7	1
Oral candidiasis	5	3
Diarrhea	1	1
Total	22	11
Clinical HIV disease (1st event)		
AIDS	8	6
Oral candidiasis	15	5
Oral hairy leukoplakia	10	5
Diarrhea	1	1
Herpes zoster	28	18
Total	62	35

Sixty-two recipients of placebo and 35 recipients of zidovudine had clinical HIV disease (relative risk, 0.55; 95 percent confidence interval, 0.37 to 0.84; P = 0.004) (Table 3 and Table 4, Figure 1). The probability of progression to clinical HIV disease at two years was 0.15 in the placebo group and 0.09 in the zidovudine group (95 percent confidence interval for the difference, -0.11 to 0.00).

Compliance

To assess compliance with study medication, the maximal mean corpuscular volumes were determined for patients receiving zidovudine and placebo. For 465 patients in the zidovudine group, the mean (±SD) maximal mean corpuscular volume was 110 ±10.5 microm^3. For 468 patients in the placebo group, the corresponding figure was 92.0 ±5.1 microm^3. Only 5 percent of the placebo recipients had maximal mean corpuscular volumes above 100 microm^3, and 10 percent of the zidovudine recipients had maximal mean corpuscular volumes below 95 microm^3.

Safety Data

Severe hematologic or clinical side effects were rare in both groups. Only three patients in the zidovudine group (0.6 percent) had a hemoglobin count of less than 8 g per deciliter, whereas only 2 percent of patients in each treatment group had neutropenia involving <750 cells per cubic millimeter. Leukopenia (<1500 cells per cubic millimeter) developed in only one patient assigned to placebo. Thrombocytopenia (<50,000 cells per cubic millimeter) occurred in seven patients receiving placebo (1 percent) and in three patients receiving zidovudine (0.6 percent).

Subjective symptoms were similar to those previously reported[2,3]. Symptoms reported more frequently in the zidovudine group included nausea (in 20 percent of the zidovudine group and 8 percent of the placebo group), headache (in 12 percent and 6 percent, respectively), asthenia (8 percent and 2 percent), and anorexia (4 percent and 1 percent). The overall symptoms reported were of mild intensity. Otherwise, the frequency of events was very low or similar in the two treatment groups.

The study treatments were well tolerated overall. Among the patients who remained in the study, 422 of 482 recipients of placebo (88 percent) and 385 of 492 recipients of zidovudine (78 percent) completed at least 90 percent of the study period without dose modification. Among the patients who did modify the dose, noncompliance was the most common reason for the initial modification, cited by 68 recipients of placebo (14 percent) and 87 recipients of zidovudine (18 percent). In only 15 of those receiving placebo (3 percent) and 35 of those receiving zidovudine (7 percent) was the first dose modification reported to be due to hematologic side effects. Subjective symptoms associated with nausea and headache (alone or in combination with other symptoms) were given as the reason for the first dose modification in 8 (2 percent) and 4 (1 percent), respectively, of the placebo recipients and 30 (6 percent) and 17 (3 percent) of the zidovudine recipients.

Discussion

In this large long-term, randomized, double-blind, placebo-controlled trial, zidovudine significantly reduced disease progression overall in patients with early asymptomatic HIV infection and CD4+ cell counts above 400 per cubic millimeter. Over a three-year period, the probability of progression to CDC group IV disease, CD4+ cell counts of less than 350 per cubic millimeter, or both was reduced by approximately half by treatment with zidovudine. These results are consistent with those of previous studies in asymptomatic HIV infection[3] and early symptomatic HIV disease[2] in patients with fewer than 500 CD4+ cells per cubic millimeter. In addition, they provide the first evidence of similar benefit for persons with early asymptomatic HIV infection whose CD4+ cell counts are above 500 per cubic millimeter and indicate that such benefits are maintained for more than 2 1/2 years in those with more than 400 CD4+ cells per cubic millimeter.

Given the necessary modifications to the protocol, it was expected that the number of patients with progression to CDC group IV disease during the study would be limited. Nevertheless, the risk of such progression was reduced by approximately half by treatment with zidovudine. Among the remaining patients in whom symptoms and signs of HIV disease developed, the End Points Committee was able to use the end point of clinical HIV disease, which included events of early HIV disease as well as those of CDC group IV disease. Nonetheless, 59 patients had events of clinical HIV disease reported by their physicians that did not meet the study criteria and were not included in the analysis of clinical HIV disease. Since these events were also approximately twice as common in the placebo group, their occurrence serves to strengthen our conclusions and to support the validity of events of clinical HIV disease as a marker of more serious progression of disease in this patient population.

The reduction in the development of clinical HIV disease was not limited to patients with lower CD4+ cell counts at base line. The hazard ratio for progression to clinical HIV disease in patients with 500 to 749 CD4+ cells per cubic millimeter indicates a reduction in the risk of almost half. Although patients with 400 to 499 CD4+ cells per cubic millimeter may be at higher immediate risk of progression of clinical disease, these data arouse concern about current guidelines for intervention that are based only on CD4+ cell counts below 500 per cubic millimeter.

Progression to CD4+ cell counts below 350 per cubic millimeter was also significantly reduced by zidovudine therapy. Overall, the risk of progression was 40 percent less in the zidovudine group than in the placebo group. As expected, patients with lower base-line CD4+ cell counts were more likely to reach this end point during the study, although similar benefits were observed in both strata of patients with less than 750 CD4+ cells per cubic millimeter (400 to 499 and 500 to 749). These data support the use of an end point based on CD4+ cell count as a surrogate marker of clinical disease progression.

The zidovudine dosage of 500 mg twice daily was selected before the efficacy of doses of 500 to 600 mg per day had been demonstrated[4,5]. It would seem reasonable to infer that lower total daily doses might have been equally effective, but it has not yet been established that they can be given in two divided doses. Despite the use of a higher daily dose of zidovudine in this study than is routinely used in current practice, the drug was well tolerated by the majority of patients. The frequency of hematologic toxicity was very low in both groups. The nature of subjective side effects was similar to that reported elsewhere[3]. Nevertheless, these findings are encouraging, because the average follow-up was almost twice as long as previously reported[3].

Concern has been expressed about the duration of benefit from zidovudine[11,12,13]. In our study clinical and immunologic effects of therapy were clearly evident at 2 1/2 years and may extend for at least 3 years. There are now data demonstrating the drug's efficacy at all stages of HIV disease apart from primary HIV infection. When all available data are considered, it is apparent that major benefit may be limited to 6 to 12 months in patients with advanced HIV disease,[7] 1 to 2 years in those with CD4+ cell counts from 200 to 400 per cubic millimeter,[15] and perhaps 2 to 3 years in those with earlier stages of HIV infection. This would be entirely consistent with the development of clinical failure in more advanced HIV disease in association with changes in virologic markers, including resistance to zidovudine[16,17,18]. All these factors argue for early intervention with zidovudine in order to obtain the most prolonged benefit and allow patients to maintain a good quality of life.

Another issue is whether early intervention would be associated with longer survival than would treatment in the advanced stages of HIV disease. One study has suggested that early treatment offers no survival benefit, but both treatment groups had relatively advanced disease and the distinction between early and late therapy appeared to be very limited[10]. A preliminary report from the Concorde study has also indicated that immediate treatment with zidovudine provided no survival advantage as compared with deferred treatment[19]. Population studies, however, have suggested that in asymptomatic patients with fewer than 200 CD4+ cells per cubic millimeter zidovudine treatment provides a survival benefit of at least six months, but this may increase with intervention at higher CD4+ cell counts[6]. Although such benefits are obviously finite, it might be expected that survival could ultimately be improved with very early antiretroviral therapy. Hence, treatment strategies now under evaluation should be addressing ways of providing a substantially more sustained response before advanced disease develops. Nevertheless, the results presented here indicate that zidovudine monotherapy in early asymptomatic HIV-infected persons with more than 400 CD4+ cells per cubic millimeter is beneficial and well tolerated.

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Source Information

From the National Centre in HIV Epidemiology and Clinical Research, St. Vincent's Hospital, University of New South Wales, Sydney, Australia (D.A.C.); Hospital Clinic I Provincial de Barcelona, Barcelona, Spain (J.M.G.); Bispebjerg University Hospital, Copenhagen, Denmark (S.K.); St. Pierre University Hospital, Brussels, Belgium (N.C.); the Wellcome Research Laboratories, Beckenham, Kent, United Kingdom (J.M., J.W.S., A.P.F.); Medizinische Poliklinik der Universitat, Munich, Germany (F.-D.G.); Ulleval University Hospital, Oslo, Norway (J.N.B.); University of Vienna Medical School, Vienna, Austria (G.S.); the Albion Street Centre, Prince of Wales Hospital, Sydney, Australia (R.L.M.); and the Instituto de Salud Carlos III, Madrid (J.G.-L.). A list of the persons and institutions participating in the European-Australian Collaborative Group appears in the Appendix.

Address reprint requests to Dr. Cooper at the National Centre in HIV Epidemiology and Clinical Research, 2nd floor, 376 Victoria St., Sydney NSW 2010, Australia.

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Appendix

The following members of the European-Australian Collaborative Group (Study 020) participated in this trial, enrolled research subjects, or both.

Australia -- National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, and St. Vincent's Hospital, Sydney: N. Bodsworth and C. D'Arcy-Evans; Albion Street Centre, Sydney: J. Gold, H. Michelmore, V. Furner, A. Pethebridge, J. Peterson, and K. Jeffords; Royal Perth Hospital: M. French, S. Mallal, and J. Hudson; Taylor Square Private Clinic, Sydney: R. Finlayson and M. Robertson; Middle Park Clinic, Melbourne: P. Meese and I. Chenoweth; P. Brooke, Sydney; Specialized Health Services, Brisbane: G.H. Ree and N. Denholm; P. Rowland, Canberra; K. Aldridge; Clinic 275, Adelaide: P. McEvoy and W. Ferguson; N. Doong, Sydney; A. Buchanan, Melbourne; C. Duncombe, Sydney; R. Liddy, Sydney (deceased); Royal Melbourne Hospital: P. Greenberg; M. Bloch, Sydney; Royal Brisbane Hospital: A. Allworth; H. Wraight, Melbourne; Sexual Health Centre, Sydney Hospital: B. Donovan; Royal Prince Alfred Hospital, Sydney: R. Garsia; Alfred Hospital, Melbourne: E. Benson and M. O'Flaherty; Sexual Health Centre, Melbourne: D. Jacobs; D. Rhodes, Adelaide; D. Chambers, Sydney; A. Mechtler, Sydney; and STD Clinic/AIDS Reference Centre, Woden Valley Hospital, Canberra: G. White.

Spain -- C.I.C. Institute of Health Carlos III, Madrid: F. Laguna, F. Diaz, and M. Adrados; Hospital Germans Trias i Pujol, Badalona: B. Clotet, A. Jou, and G. Sirera; Hospital Clinic I Provincial, Barcelona: J. Mallolas, J.M. Miro, and L. Zamora; Hospital de la Seguridad Social `Virgen del Rocio,' Seville: M. Leal and A. Sanchez-Quijano; Hospital de Bellvitge `Principes de Espana,' Barcelona: D. Podzamczer and F. Gudiol; Ciudad Sanitaria `La Fe,' Valencia: J.L. Aldeguer and J. Lacruz-Rodrigo; Hospital de la Princesa, Madrid: I. Santos and A. Noguerado; Centro Especial `Ramon y Cajal,' Madrid: L. Buzon; and Hospital Mutua de Terrassa, Barcelona: C. Estany.

Belgium -- St. Pierre University Hospital, Brussels: M. Gerard and M.E. Payen; Institute of Tropical Medicine, Antwerp: P. Piot and M. Vandenbruaene; St. Luc-UCL, Brussels: B. Van der Cam and S. Shawkey; Hopital St. Joseph, Liege: P. Henrivaux; Gasthuisberg, Louvain: H. Bobbaers; Institut Medico-Chirurgical, Brussels: H. Bondue; Hopital Civil, Charleroi: J.C. Legrand; Hopital Erasme, Brussels: C.M. Farber; and U.Z Gent, Ghent: F. Soete.

Denmark -- Bispebjerg Hospital, Copenhagen: A.-M. Worm and B.L. Jensen; Rigshospitalet, Copenhagen: K. Krogsgaard and G. Vejlsgaard; and Marselisborg Hospital, Aarhus: T. Seefeldt.

Germany -- Universitatsklinikum, Essen: M. Goos and P. Mertins; Medizinische Klinik und Poliklinik der Universitat, Munich: J.R. Bogner; and Landesinstitut fur Tropenmedizin, Berlin: F. Janike.

Luxembourg -- Centre Hospitalier de Luxembourg: R. Hemmer.

Norway -- Ulleval University Hospital, Oslo: A. Maeland.

Austria -- University of Vienna Medical School: S. Mayerhofer.

Finland -- Aurora Hospital, Helsinki: J. Lahdevirta.

Iceland -- Reykjavik City Hospital: S. Gudmundsson.

United Kingdom -- Wellcome Research Laboratories: J. Yeo and C. Romero.

Related Letters:

Zidovudine in Asymptomatic HIV Infection
Phillips A. N., Sabin C. A., Berger P. B., Martinez R., Cooper D. A., Gatell J. M.

N Engl J Med 1993; 329:1895-1896, Dec 16, 1993. **Correspondence**

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