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A RANDOMIZED TRIAL OF THREE ANTIPNEUMOCYSTIS AGENTS IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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Abstract Background. We evaluated the effectiveness of three treatment strategies for the prevention of a first episode of *Pneumocystis carinii* pneumonia in patients infected with the human immunodeficiency virus (HIV).

Methods. In an open-label trial, 843 patients with HIV infection and fewer than 200 CD4+ cells per cubic millimeter received zidovudine plus one of three randomly assigned prophylactic agents, beginning with trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine and followed by a defined sequence of other drugs to be used in cases of intolerance.

Results. The estimated 36-month cumulative risks of *P. carinii* pneumonia were 18 percent, 17 percent, and 21 percent in the trimethoprim-sulfamethoxazole, dapsone, and aerosolized-pentamidine groups, respectively ($P=0.22$). The difference in risk among treatment strategies was negligible in patients entering the study with 100 or more CD4+ lymphocytes per cubic millimeter. In those entering with fewer than 100 CD4+ cells per cubic millimeter, the risk was 33 percent with aerosolized pentami-

dine, as compared with 19 percent with trimethoprim-sulfamethoxazole and 22 percent with dapsone ($P=0.04$). The lowest failure rates occurred in patients receiving trimethoprim-sulfamethoxazole, and failures were more common with 50 mg of dapsone than with 100 mg. Toxoplasmosis developed in less than 3 percent of patients. Of the patients assigned to the two systemic therapies, only 23 percent were receiving their assigned drug and dose when they completed the study. The median survival was approximately 39 months in all three groups, and the mortality attributable to *P. carinii* pneumonia was only 1 percent.

Conclusions. In patients with advanced HIV infection, the three treatment strategies we examined have similar effectiveness in preventing *P. carinii* pneumonia. Strategies that start with trimethoprim-sulfamethoxazole or with high-dose dapsone, rather than aerosolized pentamidine, are superior in patients with fewer than 100 CD4+ lymphocytes per cubic millimeter. (N Engl J Med 1995;332:693-9.)

SEVERAL forms of chemoprophylaxis can prevent *Pneumocystis carinii* pneumonia and thereby improve survival in persons with advanced human immunodeficiency virus (HIV) disease.¹⁻⁹ Trimethoprim-sulfamethoxazole, the most widely recommended drug, can also protect against toxoplasmosis and is inexpensive, but it is poorly tolerated in this population.^{2,5,10-13} Aerosolized pentamidine has the advantages of excellent tolerability and once-monthly dosing, but it is less

active than trimethoprim-sulfamethoxazole.^{3-6,10,12} Dapsone, an inexpensive sulfone, appears to be at least as active as aerosolized pentamidine, and it is better than that drug in preventing toxoplasmosis when given in combination with pyrimethamine.¹⁴⁻¹⁷

Despite a large number of studies, the relative effectiveness and clinical usefulness of the different preventive strategies have not been adequately evaluated, because a large and lengthy trial is required to assess the effect of factors such as compliance, long-term tolerance, and ongoing antiretroviral treatment. We report the results of such a trial — AIDS Clinical Trials Group (ACTG) 081.

METHODS

Study Design

Patients were randomly assigned to one of three open-label treatments within strata based on prior zidovudine use, institution, and intention to participate in a nested study (ACTG 981), the results of which are reported elsewhere in this issue of the *Journal*.¹⁸ In addition to standard-dose zidovudine, the treatments consisted of three prophylactic drugs given initially, followed by a defined sequence of other drugs and doses to be used in cases of intolerance. The initial drugs were trimethoprim-sulfamethoxazole (one double-strength tab-

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let [containing 160 mg of trimethoprim and 800 mg of sulfamethoxazole] twice daily by mouth), dapsone (50 mg twice daily by mouth), and aerosolized pentamidine (300 mg every four weeks, administered by a Respigard II nebulizer).

The protocol was reviewed and approved by the local institutional review boards, and all patients gave written informed consent. All were HIV-infected persons at least 13 years of age who had had CD4+ lymphocyte counts below 200 per cubic millimeter at least once but no history of *P. carinii* pneumonia or toxoplasmosis. All had tolerated at least one month of zidovudine therapy at a dose of at least 500 mg daily, and none had active bacterial or mycobacterial infections. All weighed at least 40 kg and had hemoglobin counts of at least 9.5 g per deciliter, absolute neutrophil counts of at least 1000 per cubic millimeter, platelet counts of at least 75,000 per cubic millimeter, creatinine clearances of more than 50 ml per minute, serum aminotransferase levels less than 10 times the upper limit of normal, and no evidence of glucose-6-phosphate dehydrogenase deficiency. None were pregnant or lactating women. None had a history of anaphylactic-type reactions to any of the study drugs or any other sulfa drugs or sulfones, none had received prophylaxis against *P. carinii* within four weeks of entry into the study, and none were receiving active primary therapy for an infection or cancer.

End Points

Summaries of all reported episodes of *P. carinii* pneumonia and toxoplasmosis were reviewed independently by the study chairs, without knowledge of the study treatment; there were no disagreements. Presumed *P. carinii* pneumonia was defined by the presence of typical pulmonary symptoms, evidence of pulmonary dysfunction, a chest radiograph compatible with the diagnosis, and a response to therapy or a death from respiratory causes in the absence of another explanation for the pulmonary syndrome. Confirmed infection with *P. carinii* was defined by the detection of organisms with standard stains. Presumed toxoplasmosis was defined by the presence of a neurologic syndrome compatible with the diagnosis, plus compatible lesions on either computed tomography or magnetic resonance imaging and either a radiographic and a clinical response to appropriate therapy or death in two to six weeks. Confirmed toxoplasmosis was defined by the detection of *Toxoplasma gondii* in brain-biopsy specimens.

Management of Toxic Effects

Toxicity was defined according to the standard ACTG grading scheme.⁵ Patients in the systemic-therapy groups who had recurring grade 3 toxic effects had their doses reduced, were then switched to the alternate systemic medication, had their doses of that medication reduced, and were then switched to therapy with aerosolized pentamidine. Patients in the aerosolized-pentamidine group who had recurring grade 3 toxic effects were switched to trimethoprim-sulfamethoxazole therapy and were then treated by dose reduction and crossover to the alternate treatment as described above. Challenges with the original drug were encouraged before therapy was changed, but patients receiving any form of therapy who had anaphylactic-type reactions were switched immediately. Starting in mid-1991, patients who reached any of the end points (i.e., in whom *P. carinii* pneumonia or toxoplasmosis developed) were given trimethoprim-sulfamethoxazole.⁵

Statistical Analysis

A sample containing 600 patients was selected to ensure 80 percent power to detect a difference of 15 percent (10 percent vs. 25 percent) in the cumulative risk of *P. carinii* pneumonia over a two-year period, with two-sided tests with an alpha level of 0.05. All the primary analyses compared the groups as defined according to the treatment assignments at randomization and including all follow-up information. As planned, the two systemic-therapy groups were combined and compared with the aerosolized-pentamidine group, and all treatments were compared between subgroups defined by base-line CD4+ counts. The cumulative risks of both efficacy and treatment failure due to toxicity were calculated from Kaplan-Meier estimates. In the analyses of the time to an event, data on patients were censored at their deaths. Treatments were compared by the log-rank test, and hazard ratios were estimated by stratified and unstratified

Cox proportional-hazards models. Unadjusted two-tailed P values are reported. The failure rate for each drug and dose was estimated as the number of events that occurred divided by the total number of patient-years associated with that treatment. Interim analyses of the study were presented to the ACTG Data and Safety Monitoring Board on five occasions; because of low event rates, the board recommended an expansion of the accrual goal on one occasion, and of the follow-up period on another.

RESULTS

Study Population and History

One of 843 registrants did not meet the indications for antipneumocystis prophylaxis and was excluded from the study. Eighty-five other patients had borderline laboratory values or variation in their schedules of zidovudine dosing; most were granted exemptions before enrollment, and the remainder were accepted into the study shortly thereafter without knowledge of their treatment assignments. A total of 842 patients were therefore studied. The median follow-up was 39 months, the total follow-up was 2058 patient-years, and data were available through the end of the study for 91 percent of the surviving participants.

The majority of the patients were white (83 percent), male (93 percent), homosexual (61 percent), and seronegative for antibody to toxoplasma (80 percent). The mean age was 36 years, and the mean CD4+ lymphocyte count 150 per cubic millimeter (Table 1). The distribution of base-line characteristics in the treatment groups was well balanced, except that a disproportionate number of patients in the aerosolized-pentamidine group registered for ACTG 981 in addition to this study (Table 1).¹⁸

P. carinii Pneumonia

Among the 137 reported cases of *P. carinii* pneumonia, 42 (31 percent) occurred in the trimethoprim-sulfamethoxazole group, 41 (30 percent) in the dapsone group, and 54 (39 percent) in the aerosolized-pentamidine group. The estimated 36-month cumulative risks of reported *P. carinii* pneumonia were 18 percent, 17 percent, and 21 percent, respectively (P=0.22 by the log-rank test for the comparison of the three groups; P=0.08 for the comparison of the combined systemic-therapy groups with the aerosolized-pentamidine group) (Fig. 1, upper panel). Among the 105 proved cases, 34 (32 percent) occurred in the trimethoprim-sulfamethoxazole group, 33 (31 percent) in the dapsone group, and 38 (36 percent) in the aerosolized-pentamidine group. The estimated 36-month cumulative risks of confirmed *P. carinii* pneumonia were 15 percent, 13 percent, and 15 percent, respectively (P=0.75 by the log-rank test). Pairwise comparisons of the treatment groups stratified according to base-line CD4+ lymphocyte counts yielded similar results (Table 2).

Among patients entering the trial with fewer than 100 CD4+ cells per cubic millimeter, the estimated 36-month cumulative risks of reported *P. carinii* pneumonia were 19 percent, 22 percent, and 33 percent in the trimethoprim-sulfamethoxazole, dapsone, and aerosolized-pentamidine groups, respectively (P=0.04 for the comparison of the three groups and P=0.06 for

Table 1. Base-Line Characteristics of the Three Treatment Groups.*

CHARACTERISTIC	TRIMETHOPRIM-SULFAMETHOXAZOLE (N=276)	DAPSONE (N=288)	AEROSOLIZED PENTAMIDINE (N=278)
Participation in ACTG 981(%)	49	48	56
Mean age	36±9	35±9	35±9
Male sex (%)	91	94	93
Antibody to <i>T. gondii</i> (%)	22	18	19
Mean CD4+ count/mm ³	148±101	152±105	153±102
CD4+ count at entry (%)			
<100 cells/mm ³	32	34	32
≥200 cells/mm ³	23	24	24
Hemoglobin (g/dl)	13.6±1.7	13.3±1.6	13.3±1.5
Platelets (×10 ⁻³ /mm ³)	227±72	230±71	225±71
Granulocytes (×10 ⁻³ /mm ³)	2.2±1.0	2.3±1.1	2.3±1.1
Aspartate aminotransferase (proportion of ULN)†	0.86±0.65	0.86±0.65	0.85±0.69
Creatinine (proportion of ULN)†	0.64±0.13	0.64±0.13	0.65±0.12

*Plus-minus values are means ±SD. All other values are percentages of the group.

†Values shown are proportions of the upper limit of normal (ULN) at participating laboratories.

the comparison of the systemic-therapy groups with the aerosolized-pentamidine group) (Fig. 1, lower panel). In comparison, the respective risks were 17 percent, 14 percent, and 15 percent among patients entering the trial with 100 or more CD4+ cells (P=0.58 and P=0.70 for the respective comparisons by the log-rank test). Thus, the absolute differences in risk, although negligible in the less immunosuppressed group, amounted to as much as 14 percent in the more immunosuppressed group.

Table 3 shows the rates of confirmed first episodes of *P. carinii* pneumonia in the study patients according to the treatment they were receiving at the onset of the episode (an "as treated" analysis). In the trimethoprim-sulfamethoxazole group, only 4 of the 34 treatment failures occurred while the patients were still receiving that drug at the original dose. The lowest rates of failure among all the subgroups were in the trimethoprim-sulfamethoxazole group among patients who were still receiving the drug at a dose of one or two tablets daily. The rates of treatment failure were higher after the patients were switched to dapsone therapy at 50 mg twice daily, and the rates rose again after the dose of dapsone was reduced to 50 mg daily. In the dapsone group, 21 of the 33 treatment failures occurred while the patients were still receiving that drug, mostly because the failure rates were four times higher after the first dose reduction. The rate of treatment failure in the dapsone group decreased after the patients were switched to trimethoprim-sulfamethoxazole therapy. Among patients assigned to aerosolized pentamidine, switching was unusual; therefore, 37 of the 38 treatment failures occurred while the patients were still receiving that drug, and there was little difference between the "as assigned" and the "as treated" rates of treatment failure. Three patients for whom dapsone was initially prescribed and one patient for whom aerosolized pentamidine was prescribed reported receiving trimethoprim-sulfamethoxazole in the month before treatment failure. In addition, patients reported some exposure to a systemic antipneumocystis agent such as one of the study drugs during 75 of the 9936 months (1 percent) in which they were sup-

posed to have received only aerosolized pentamidine.

Hospitalization was required in 80 percent of the patients with *P. carinii* pneumonia, and seven patients died within one month of diagnosis. Five of these deaths were attributed to *P. carinii* pneumonia. Hospitalizations, deaths, and deaths attributable to *P. carinii* pneumonia were distributed approximately equally among the treatment groups.

Toxoplasmosis

Among 24 reported cases of toxoplasmosis, 9 each (38 percent) occurred in the trimethoprim-sulfamethoxazole and the aerosolized-pentamidine groups, and 6 (25 percent) occurred in the dapsone group. The overall risk of toxoplasmosis was 2 to 3 percent, and the risk among the 169 patients seropositive for antibody to *T. gondii* was about 12 percent in each treatment group. Four of the nine cases in the trimethoprim-sulfamethoxazole group, two of the six cases in the dapsone group, and all nine cases in the aerosolized-pentamidine group oc-

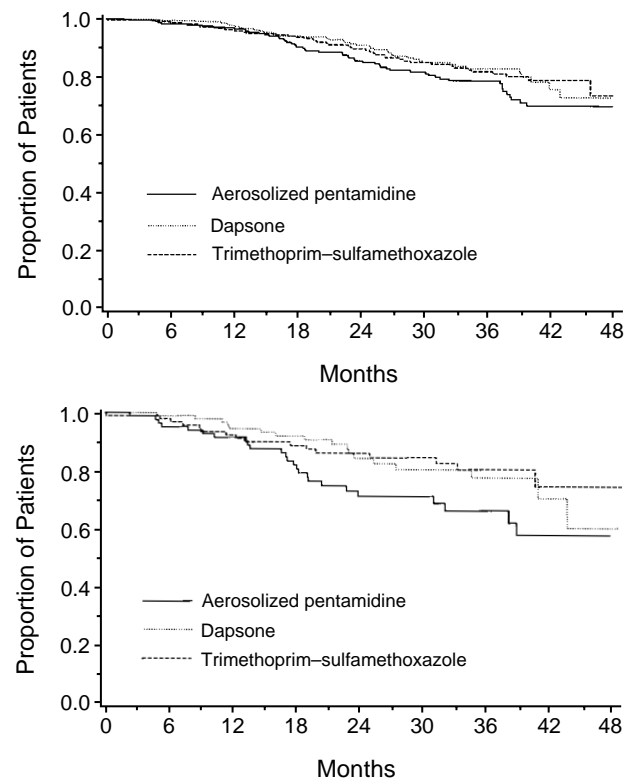


Figure 1. Cumulative Risk of a Reported First Episode of *P. carinii* Pneumonia, According to the Assigned Treatment, among All Patients (Upper Panel) and among Patients Entering the Study with Fewer Than 100 CD4+ Cells per Cubic Millimeter (Lower Panel).

The cumulative risk for recipients of trimethoprim-sulfamethoxazole is similar in both panels, but the risk for recipients of aerosolized pentamidine and the differences in risk among the three regimens are greater in the lower panel.

curred in patients still receiving the initially assigned drug. Overall, 5 cases occurred in patients receiving trimethoprim-sulfamethoxazole, 5 in patients receiving dapsone, and 14 in patients receiving aerosolized pentamidine. The nine proved cases of toxoplasmosis were similarly distributed.

Mortality

Four hundred three participants (48 percent) died during the study. The median durations of survival in the trimethoprim-sulfamethoxazole, dapsone, and aerosolized-pentamidine groups were 40, 39, and 37 months, respectively ($P=0.78$ by the log-rank test) (Table 2). The median times to a critical event (*P. carinii* pneumonia, toxoplasmosis, or death) were 37, 35, and 40 months in the respective groups ($P=0.55$) (Table 2). Differences in mortality between the patients receiving aerosolized pentamidine and those receiving the systemic therapies were greater among patients who entered the study with fewer than 100 CD4+ lymphocytes per cubic millimeter (data not shown).

Toxic Effects

Only 21 percent of the trimethoprim-sulfamethoxazole group and 25 percent of the dapsone group completed the study receiving their originally assigned drug at the original dose, as compared with 88 percent of the aerosolized-pentamidine group. No change other than a dose reduction was required for 28 percent of the trimethoprim-sulfamethoxazole group and 33 percent of the dapsone group. An additional 27 percent of the trimethoprim-sulfamethoxazole group was switched to dapsone, 20 percent of the dapsone group was switched to trimethoprim-sul-

Table 3. Rates of Confirmed First Episodes of *P. carinii* Pneumonia, According to the Assigned Treatment and the Treatment Being Received at Diagnosis.*

TREATMENT RECEIVED AT DIAGNOSIS	ALL PATIENTS	ASSIGNED TO TMP-SMX	ASSIGNED TO DAPSONE	ASSIGNED TO AEROSOLIZED PENTAMIDINE
As assigned†				
No. of episodes	105	34	33	38
Patient-years	2058	690	696	672
Rate	5.1	4.9	4.7	5.7
Full dose				
Treatment	—	TMP-SMX twice daily	Dapsone twice daily	Aerosolized pentamidine
No. of episodes	51	4	10	37
Patient-years	1367	334	382	651
Rate	3.7	1.2	2.6	5.7
1st Dose reduction				
Treatment	—	TMP-SMX daily	Dapsone daily	Not applicable
No. of episodes	11	0	11	—
Patient-years	188	91	97	—
Rate	5.9	0	11.3	—
1st Switch				
Treatment	—	Dapsone twice daily	TMP-SMX twice daily	TMP-SMX twice daily
No. of episodes	13	10	2	1
Patient-years	162	106	45	11
Rate	8.0	9.4	4.4	9.1
2nd Dose reduction				
Treatment	—	Dapsone daily	TMP-SMX daily	TMP-SMX daily
No. of episodes	8	7	1	0
Patient-years	62	40	21	1
Rate	12.9	17.5	4.8	0
2nd Switch				
Treatment	—	Aerosolized pentamidine	Aerosolized pentamidine	Dapsone twice daily
No. of episodes	18	11	7	0
Patient-years	179	85	92	2
Rate	10.1	12.9	7.6	0

*Rates shown are per 100 patient-years. Single doses of the systemic drugs are 50 mg of dapsone and one double-strength tablet of trimethoprim-sulfamethoxazole (TMP-SMX). No statistical tests were performed on these data because of the confounding effects of treatment assignment, characteristics of patients, judgments by providers, and progression of disease between switches.

†Four patients included in the "as assigned" analysis do not appear elsewhere, either because they were receiving treatment out of sequence or because they were being treated with drugs not included in the protocol.

famethoxazole, and 4 percent of the aerosolized-pentamidine group was switched to trimethoprim-sulfamethoxazole because of toxicity. An additional 20 percent, 18 percent, and 0 percent of the respective groups were switched a second time. Switching continued throughout the trial, with a median of 2.5 years to the first switch in the systemic-therapy groups (Fig. 2). The patients in these groups spent 88 percent of a total of 1386 person-years of follow-up receiving systemic therapy, whereas the patients assigned to aerosolized pentamidine spent 98 percent of 672 person-years of follow-up receiving that drug.

In the trimethoprim-sulfamethoxazole group, the serious toxic effects that at least 10 percent of patients reported before switching were leukopenia (26 percent of reports), fever (20 percent), rash (16 percent), and gastroenterologic distress (10 percent); in addition, anaphylaxis was reported in two persons (2 percent of reports). In the dapsone group, serious toxic effects reported before switching were leukopenia (24 percent of reports), anemia (21 percent), elevations in serum aminotransferase levels (13 percent), fever (13 percent), and gastroenterologic distress (11 percent); in addition, serious methemoglobinemia and

Table 2. Relative Risk of *P. carinii* Pneumonia and Toxoplasmosis.*

END POINT	TMP-SMX vs. DAPSONE	TMP-SMX vs. AEROSOLIZED PENTAMIDINE	DAPSONE vs. AEROSOLIZED PENTAMIDINE
	relative risk (95% CI)		
<i>P. carinii</i> pneumonia			
Reported	1.0 (0.6–1.5)	1.4 (0.7–2.1)	1.4 (0.9–2.1)
Confirmed	1.0 (0.6–1.6)	1.2 (0.8–1.9)	1.2 (0.7–1.9)
Toxoplasmosis, reported	0.7 (0.3–2.1)	1.1 (0.4–2.8)	1.5 (0.5–4.3)
Death	1.1 (0.9–1.4)	1.1 (0.9–1.5)	1.0 (0.8–1.3)
Death or reported <i>P. carinii</i> pneumonia or toxoplasmosis	1.1 (0.9–1.4)	1.2 (1.0–1.5)	1.1 (0.9–1.4)

*Values shown are overall estimates obtained from stratified Cox regressions. TMP-SMX denotes trimethoprim-sulfamethoxazole, and CI confidence interval.

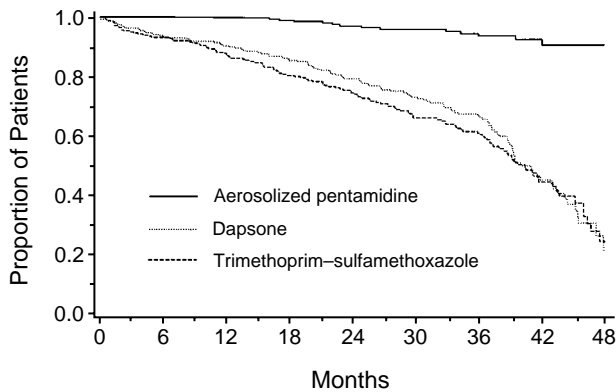


Figure 2. Time to the First Switch in Prophylactic Medication, According to the Assigned Treatment.

the sulfone syndrome were reported in one person each (1 percent each).¹⁹

Over half of all participants had at least one grade 3 adverse event. Grade 3 fever and nausea were more common in the trimethoprim-sulfamethoxazole group (in 25 and 14 percent of patients, respectively) and the dapsone group (29 and 16 percent) than in the aerosolized-pentamidine group (19 and 9 percent; $P=0.02$ for the comparison of the three groups and $P=0.06$ for the comparison of the systemic-therapy groups with the aerosolized-pentamidine group). Rash was most common in the trimethoprim-sulfamethoxazole group (16 percent), but it was more common in the dapsone group (9 percent) than in the aerosolized-pentamidine group (5 percent) ($P=0.001$ and $P=0.04$ for the respective comparisons). Pancreatitis occurred in eight patients in the trimethoprim-sulfamethoxazole group, eight in the dapsone group, and six in the aerosolized-pentamidine group; two, three, and five of these patients, respectively, were still receiving their assigned drugs at the time of the attack.

The proportions of patients who had any grade 3 hematologic toxic effects were similar in the three groups (trimethoprim-sulfamethoxazole, 47 percent; dapsone, 47 percent; and aerosolized pentamidine, 43 percent), as were the proportions who had grade 3 toxic effects on hemoglobin levels (20 percent, 25 percent, and 21 percent, respectively; $P=0.18$) and the proportions who received a transfusion of red cells (17 percent, 20 percent, and 16 percent, respectively; $P=0.43$). However, the rates of grade 3 toxic effects on hemoglobin levels were higher in the dapsone group (30 per 100 patient-years, as compared with 21 for trimethoprim-sulfamethoxazole and 17 for aerosolized pentamidine [$P\leq 0.01$ for all pairwise comparisons]). Grade 3 toxic effects on granulocyte counts were more common in the systemic-therapy groups (trimethoprim-sulfamethoxazole, 40 percent; dapsone, 34 percent; and aerosolized pentamidine, 28 percent; $P=0.01$), and the relative rates were also different (75 per 100 patient-years for trimethoprim-sulfamethoxazole, as compared with 65 for dapsone and 34 for aerosolized pentamidine; $P\leq 0.01$ for all pairwise comparisons). Nonetheless, the median duration of zidovudine use was similar in the

three treatment groups (trimethoprim-sulfamethoxazole, 15 months; dapsone, 14 months; and aerosolized pentamidine, 17 months; $P=0.45$).

DISCUSSION

Although most prior evidence has suggested that trimethoprim-sulfamethoxazole is the preferred initial prophylaxis in all HIV-infected patients at risk for *P. carinii* pneumonia, our results indicate that initially prescribing dapsone and initially prescribing aerosolized pentamidine each lead to similar outcomes. Factors associated with the study design probably account for these somewhat surprising findings. Previous studies, which have focused on the biologic efficacy of the drugs and have been relatively small or short-term, emphasized observation during treatment or were conducted in high-risk patients.^{2,4,6,11-15,20,21} In contrast, this trial evaluated the clinical effectiveness of the three treatment strategies. It was a large and lengthy trial that attempted to minimize attrition and maintain clinical relevance by giving the drugs in concert with a flexible regimen of antiretroviral therapy to essentially all patients presenting with indications for the study treatments; in addition, it permitted simultaneous enrollment in other compatible studies.

This design permitted two key observations. First, the overall three-year risk of breakthrough *P. carinii* pneumonia was 25 percent among patients entering the study with fewer than 100 CD4+ lymphocytes per cubic millimeter, as compared with 15 percent in those entering with higher counts, because the difference in risk between the systemic therapies and aerosolized-pentamidine therapy was greater with increasing vulnerability to *P. carinii* pneumonia. In fact, the decreased effectiveness of aerosolized pentamidine in the subgroup with low CD4+ counts accounted for most of the observed differences among treatments. Second, the development of new intolerance to systemic therapies was observed throughout the study period, with the median time to a switch being 2.5 years among the patients assigned to dapsone or trimethoprim-sulfamethoxazole. About 20 percent of the patients assigned to systemic therapy switched treatments twice and completed the trial receiving aerosolized pentamidine.

Thus, because of continuing crossovers and dose reductions as the trial progressed, more patients were receiving less adequate treatments even as their vulnerability to *P. carinii* pneumonia increased. Several observations support this interpretation: the CD4+ lymphocyte counts were much lower at the time of treatment failure than at study entry (data not shown), the rates of treatment failure were higher after patients were switched to a drug than after patients were assigned to it, and the study patients spent the least time receiving trimethoprim-sulfamethoxazole and the most time receiving aerosolized pentamidine. This apparent requirement for more vigorous therapy when the host response is inadequate is reminiscent of the situation with many other long-recognized conditions, such as infectious endocarditis. In HIV disease, this principle is implicit in the recommendations for the selective

chemoprophylaxis of persons at higher risk, and it applies in the nested study ACTG 981, which showed that there is a substantial benefit with prophylaxis of HIV-related invasive fungal infection only among patients with fewer than 50 CD4+ lymphocytes per cubic millimeter.¹⁸

The possibility that initial treatment with trimethoprim-sulfamethoxazole might have been superior if tolerance had been better raises the issues of dosing and blinding. Over the short term, 3 to 7 double-strength tablets of trimethoprim-sulfamethoxazole per week are tolerated better than the initial dose of 14 double-strength tablets per week used here.^{17-19,22} However, we doubt that different initial dosing would have had much effect, because dose reductions and rechallenges were allowed liberally, because very few patients switched therapy without a trial of the initial medication at a lower dose, and because our results were similar to those of a smaller two-group study that used seven tablets per week.²³ The unblinded design, which the protocol team and community advisors thought was essential to success, undoubtedly had some effects, but it is doubtful that it accelerated switching to the extent needed to alter the conclusions. Switching continued long after the bias among physicians and patients was strongly in favor of systemic therapy, very few patients switched therapy without a rechallenge, and those assigned to a systemic-therapy group spent 88 percent of their time during the study receiving systemic therapy.

Inferences from the analysis of end points according to the therapy the patients were receiving at the time of treatment failure are limited by confounding factors, but comparisons of rates of failure after a switch from trimethoprim-sulfamethoxazole to dapsone and the reverse suggest that trimethoprim-sulfamethoxazole is the more active drug. Also, comparing rates of treatment failure after dose reductions suggests that two tablets of trimethoprim-sulfamethoxazole offer little advantage over one, but that 100 mg of dapsone is more active than 50 mg.

Inferences about the effectiveness of the study drugs as prophylaxis against toxoplasmosis are limited by a low power to detect differences because of the low seroprevalence of *T. gondii* and low incidence of toxoplasmosis in this cohort. For example, the nonsignificant relative risk of 1.5 associated with aerosolized pentamidine as compared with dapsone is similar to the relative risk of 1.8 reported in a study demonstrating the superiority of dapsone plus pyrimethamine.¹⁷ And the 3 percent incidence of disease in the trimethoprim-sulfamethoxazole group is far less than the 6 percent upper bound of the 95 percent confidence interval for the incidence of toxoplasmosis in a study showing the superiority of trimethoprim-sulfamethoxazole over aerosolized pentamidine.²⁴

In summary, outcomes after assignment to any of our treatment strategies were similar. The average attack rate of *P. carinii* pneumonia was 7 percent per year, the case fatality rate was 7 percent, and *P. carinii* pneumonia accounted for only 1 percent of all deaths. These data suggest that the greatest gains in the prevention

of *P. carinii* pneumonia are likely to come from identifying more persons at risk, rather than optimizing the therapy of those already receiving care. However, optimizing therapy remains an important goal, and our data raise the possibility that an improved strategy might try to limit the intolerance to trimethoprim-sulfamethoxazole or to reserve that treatment for the most vulnerable patients. That is, staged strategies and other approaches should be explored, and the uniform preference for trimethoprim-sulfamethoxazole as the initial preventive therapy in patients at lower risk should be reconsidered.

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APPENDIX

In addition to the study authors, the following institutions and investigators participated in the study. (The numbers in parentheses indicate the numbers of patients enrolled at each site.) *University of Cincinnati* (79) — J. Leonard, P. Daniel, W. Cotton, and S. Kohrs; *Washington University* (61) — M. Gould, M. Meyers, and M. Royal; *Harvard University* (57) — J.D. Allen, C.S. Crumpacker, and M.M. White; *University of California, San Diego* (55) — D.D. Richman, R. Haubrich, and J. Coffman; *Johns Hopkins University* (49) — R.L. Becker, L. Grue, V. Rexroad, and M. Smith; *Hershey Medical Center* (39) — W.C. Ehmann, J. Zurlo, and M. Kreher; *University of Miami Reserve University* (37) — V. Paul-Jarrett, V. Cargill, and S. Birdsong; *Ohio State University* (36) — R.J. Fass, M.F. Para, and C. Jackson; *Duke University* (34) — H. Waskin, J. Bartlett, and R. Dodge; *Northwestern University-Rush Medical College* (33) — R. Murphy, C. Benson, H. Kessler, and J. Phair; *University of Washington* (33) — T. Hooton, A. Collier, and L. Corey; *University of North Carolina* (32) — R. Whitten, B. Longmire, and C. van der Horst; *Tulane University* (31) — N. Hyslop; *University of Rochester* (29) — R.C. Reichman, D.C. Blair, and R.G. Hewitt; *Albert Einstein College of Medicine* (26) — B. Zingmen, N. Steigbigel, and J. Schliozberg; *Stanford University* (20) — T. Merrigan; *Mt. Sinai School of Medicine* (18) — D. Mildvan, C. Sanders, and C. Alder; *St. Luke's-Roosevelt Hospital Center* (18) — G.F. McKinley, M.H. Grieco, and J.L. Rivera; *University of California, San Francisco* (18) — S. Safran, R. Mah, and R. Coleman; *University of Minnesota* (18) — C. Jones, R. Nelson, and W.K. Henry; *Indiana University* (14) — J. Craft and L.J. Wheat; *State University of New York at Stony Brook* (12) — J. Fuhrer, R.T. Steigbigel, and R. Tenzler; *University of Massachusetts* (9) — S.H. Cheeseman, R.A. Koup, and K.K. Lai; *University of Southern California* (7) — F. Sattler, J. Leedom, and S. Nichols; and *UCLA-Sepulveda Veterans Affairs Medical Center* (4) — M.B. Goetz and B. Manchester.

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