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Atovaquone Compared with Dapsone for the Prevention of Pneumocystis carinii Pneumonia in Patients with HIV Infection Who Cannot Tolerate Trimethoprim, Sulfonamides, or Both

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ATOVAQUONE COMPARED WITH DAPSONE FOR THE PREVENTION OF *PNEUMOCYSTIS CARINII* PNEUMONIA IN PATIENTS WITH HIV INFECTION WHO CANNOT TOLERATE TRIMETHOPRIM, SULFONAMIDES, OR BOTH

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ABSTRACT

Background Although trimethoprim-sulfamethoxazole is the drug of choice for the prevention of *Pneumocystis carinii* pneumonia, many patients cannot tolerate it and must switch to an alternative agent.

Methods We conducted a multicenter, open-label, randomized trial comparing daily atovaquone (1500-mg suspension) with daily dapsone (100 mg) for the prevention of *P. carinii* pneumonia among patients infected with the human immunodeficiency virus who could not tolerate trimethoprim-sulfamethoxazole. The median follow-up period was 27 months.

Results Of 1057 patients enrolled, 298 had a history of *P. carinii* pneumonia. *P. carinii* pneumonia developed in 122 of 536 patients assigned to atovaquone (15.7 cases per 100 person-years), as compared with 135 of 521 in the dapsone group (18.4 cases per 100 person-years; relative risk for atovaquone vs. dapsone, 0.85; 95 percent confidence interval, 0.67 to 1.09; $P=0.20$). The relative risk of death was 1.07 (95 percent confidence interval, 0.89 to 1.30; $P=0.45$), and the relative risk of discontinuation of the assigned medication because of adverse events was 0.94 (95 percent confidence interval, 0.74 to 1.19; $P=0.59$). Among the 546 patients who were receiving dapsone at base line, the relative risk of discontinuation because of adverse events was 3.78 for atovaquone as compared with dapsone (95 percent confidence interval, 2.37 to 6.01; $P<0.001$); among those not receiving dapsone at base line, it was 0.42 (95 percent confidence interval, 0.30 to 0.58; $P<0.001$).

Conclusions Among patients who cannot tolerate trimethoprim-sulfamethoxazole, atovaquone and dapsone are similarly effective for the prevention of *P. carinii* pneumonia. Our results support the continuation of dapsone prophylaxis among patients who are already receiving it. However, among those not receiving dapsone, atovaquone is better tolerated and may be the preferred choice for prophylaxis against *P. carinii* pneumonia. (N Engl J Med 1998;339:1889-95.)

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THE prevention of *Pneumocystis carinii* pneumonia has had a substantial influence on the course of human immunodeficiency virus (HIV) disease.^{1,2} Although trimethoprim-sulfamethoxazole is the treatment of choice for prophylaxis against *P. carinii* pneumonia, intolerance often limits its use and makes it necessary to use alternative regimens.³ Dapsone, alone or in combination with pyrimethamine, is a commonly recommended prophylactic regimen for *P. carinii* pneumonia in patients who cannot tolerate trimethoprim-sulfamethoxazole.⁴ Dapsone plus pyrimethamine has been shown to be superior to aerosolized pentamidine for the prevention of toxoplasmosis.⁵ However, dapsone has limitations: it is less effective than trimethoprim-sulfamethoxazole for the prevention of *P. carinii* pneumonia and is associated with a high rate of intolerance.^{6,7}

Atovaquone, an agent with antipneumocystis activity in studies in animals,⁸ has been shown to be effective and reasonably well tolerated for the treatment of mild-to-moderate *P. carinii* pneumonia in HIV-infected patients.⁹ However, there have been no large studies of the efficacy and tolerability of atovaquone for the prevention of *P. carinii* pneumonia.

The Community Program for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG) initiated a randomized study comparing atovaquone suspension with dapsone for the prevention of *P. carinii* pneumonia among HIV-infected

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*Participants in the study are listed in the Appendix.

patients who could not tolerate trimethoprim, sulfonamides, or both.

METHODS

Study Population

HIV-infected patients 13 years of age or older were eligible for the study if they had a history of *P. carinii* pneumonia (this group received secondary prophylaxis), or if they had no history of *P. carinii* pneumonia and had a CD4+ lymphocyte count no higher than 200 per cubic millimeter or no more than 15 percent of the total lymphocyte count (this group received primary prophylaxis). Patients were also required to have a history of a treatment-limiting reaction to sulfonamides or trimethoprim, no history of intolerance of dapsone or atovaquone, and adequate glucose-6-phosphate dehydrogenase levels.

Study Design

The study was a randomized, open-label clinical trial comparing the efficacy of atovaquone (Mepron, Glaxo Wellcome, Research Triangle Park, N.C.; given as a 1500-mg suspension once daily) and dapsone (Jacobus Pharmaceuticals, Princeton, N.J.; 100-mg tablets, given once daily) in delaying or preventing the onset of confirmed or probable *P. carinii* pneumonia. Patients randomly assigned to receive dapsone who had CD4+ cell counts under 100 per cubic millimeter and positive results on serologic tests for toxoplasma were encouraged to take pyrimethamine (50 mg) and leucovorin (15 mg) each week. Patients in whom *P. carinii* pneumonia developed or who had an adverse event necessitating the discontinuation of the assigned treatment could be switched to the other study treatment. Patients were randomly assigned to treatment in a 1:1 ratio according to a permuted-block design, with stratification according to the clinical center, history with respect to *P. carinii* pneumonia, and serologic status with respect to toxoplasma.

The sample size and duration of follow-up (18 months from the time the last patient was enrolled) were calculated to provide the study with 80 percent power to detect a 50 percent decrease in the risk of *P. carinii* pneumonia among the patients assigned to atovaquone, as compared with those assigned to dapsone, at a 0.05 level of significance (in a two-sided test). It was assumed that *P. carinii* pneumonia would develop in 20 percent of the patients receiving dapsone for primary prophylaxis and in 40 percent of those receiving dapsone for secondary prophylaxis. It was also assumed that 80 percent of the participants would receive primary and secondary prophylaxis, respectively. The study was approved by each medical center's institutional review board, and the participants were required to provide written informed consent in order to participate.

End Points and Follow-up

The primary end point was the development of confirmed or probable *P. carinii* pneumonia. Confirmation required histologic or cytologic identification of *P. carinii* in bronchoalveolar-lavage, lung-biopsy, or sputum specimens. A probable diagnosis was based on a history of either exertional dyspnea or nonproductive cough; evidence of diffuse bilateral pulmonary disease on either a chest roentgenogram or a gallium scan, or abnormal arterial-blood gases; and the absence of another condition that could account for the findings. The end points were reviewed by a clinical-events committee whose members were unaware of the patients' treatment assignments. The secondary end points were intolerance of the study drug necessitating the permanent discontinuation of the drug, death, the combined end point of *P. carinii* pneumonia or death, and confirmed or probable toxoplasmosis. A four-point scale was used to grade the severity of adverse events (grade 4 events were severe and potentially life-threatening).

Statistical Analysis

Investigators were unaware of all interim results, which were reviewed by an independent data and safety monitoring board. The treatment groups were compared by means of Kaplan-Meier event-time curves, log-rank tests, and proportional-hazards regression models.¹⁰ Primary analyses were performed according to the intention-to-treat principle and were stratified according to the trial group (CPCRA or ACTG), history with respect to *P. carinii* pneumonia, and results of serologic tests for toxoplasma. Relative risks (atovaquone vs. dapsone) are given with 95 percent confidence intervals. Secondary analyses were also performed. In an "on-treatment" analysis, follow-up data were censored 30 days after the assigned study treatment was discontinued. In a second analysis, which was conducted because of the low rate of *P. carinii* pneumonia during the later follow-up period, follow-up data were censored when therapy was initiated with protease inhibitors. The proportional-hazards model was used to estimate the risk of *P. carinii* pneumonia for patients who discontinued the study treatment as compared with those who did not. In this analysis, a single time-varying indicator of discontinuation of all study treatment was included in the regression model. All P values are two-tailed; all median times reported account for censoring.

RESULTS

Characteristics of the Patients

Between October 4, 1994, and May 5, 1995, 1057 patients were enrolled in the study, 194 from 11 CPCRA units and 863 from 37 ACTG units. The two treatment groups were well balanced with regard to base-line characteristics (Table 1). Overall,

TABLE 1. BASE-LINE CHARACTERISTICS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	ATOVAQUONE (N=536)	DAPSONE (N=521)
Mean age (yr)	38.4	37.8
Female sex (%)	11.2	13.6
Race or ethnic group (%)		
Black	20.5	23.2
Hispanic	11.8	12.5
White	65.7	62.8
Other	2.1	1.5
History of injection-drug use (%)	18.6	16.9
Antiretroviral therapy (%)	57.5	59.5
PCP prophylaxis at randomization (%)	74.4	72.4
Dapsone	53.2	50.1
Pentamidine	17.9	19.2
Other	2.6	2.5
Adverse reaction to TMP-SMX (%)		
Hypersensitivity	82.5	78.7
Gastrointestinal symptoms	6.9	8.8
Hematologic abnormalities	3.7	5.8
Other	6.9	6.7
Prior diagnosis of AIDS (%)	49.6	47.6
Prior PCP (%)	28.7	27.6
Positive toxoplasma titer (%)	16.2	15.9
Mean Karnofsky score	87.7	87.7
Median CD4+ count (cells/mm ³)	55	65

*PCP denotes *Pneumocystis carinii* pneumonia, TMP-SMX trimethoprim-sulfamethoxazole, and AIDS the acquired immunodeficiency syndrome.

21.9 percent were black, 12.1 percent were Hispanic, 17.7 percent were injection-drug users, and 12.4 percent were female. A history of *P. carinii* pneumonia was reported by 298 patients (28.2 percent). Overall, the median base-line CD4+ lymphocyte count was 60 per cubic millimeter, and 16.1 percent of the patients had positive serologic tests for toxoplasma. At base line, 73.4 percent of the patients were receiving prophylaxis against *P. carinii* pneumonia (51.7 percent were receiving dapsone, 18.5 percent pentamidine, and 3.2 percent other treatments or a combination of treatments), and 58.6 percent of the patients were receiving antiretroviral treatment (46.9 percent were receiving nucleoside monotherapy, and 11.7 percent nucleoside combination therapy). At the 12-month follow-up visit, 70.5 percent of the patients were receiving antiretroviral therapy, with 31.3 percent receiving combination nucleoside therapy. At the 24-month follow-up visit, 93.0 percent of the patients were receiving antiretroviral therapy, with 17.2 percent taking combination nucleoside regimens and 71.9 percent (71.7 percent of the atovaquone group and 72.0 percent of the dapsone group) using regimens containing protease inhibitors.

Duration of Follow-up and Study Treatment

At the end of the study, on April 11, 1997, the median follow-up was 27 months for each treatment group. At this time, the status with respect to *P. carinii* pneumonia was unknown for 5.0 percent of patients assigned to atovaquone and 7.1 percent of those assigned to dapsone. The vital status of 5.0 percent of the patients in the atovaquone group and 6.7 percent of those in the dapsone group was unknown.

Of the 617 patients who were alive at the close of the study, 289 (47 percent) were receiving study-supplied dapsone or atovaquone: 214 (35 percent) were still taking the originally assigned drug, and 75 (12 percent) had been switched to the alternative treatment. The median time during which patients took the assigned drug was 7.2 months for atovaquone and 7.4 months for dapsone. The median time during which they took either the assigned drug or the alternative was 10.8 months for those assigned to atovaquone and 11.9 months for those assigned to dapsone (P=0.22).

***P. carinii* Pneumonia**

A total of 257 patients had at least one episode of confirmed or probable *P. carinii* pneumonia: 122 in the atovaquone group (15.7 cases per 100 person-years) and 135 in the dapsone group (18.4 per 100 person-years; relative risk for atovaquone vs. dapsone, 0.85; 95 percent confidence interval, 0.67 to 1.09; P=0.20) (Table 2). The cumulative percentages of patients who had had at least one episode of confirmed or probable *P. carinii* pneumonia after 6, 12, and 24 months were 8.9 percent, 19.5 percent, and 26.5 percent for patients assigned to atovaquone and 13.5 percent, 21.3 percent, and 29.5 percent for patients assigned to dapsone (Fig. 1). In both treatment groups, the risk of *P. carinii* pneumonia declined after the first year of follow-up. The relative risk of *P. carinii* pneumonia in the two groups did not differ significantly when data were censored at the time of initiation of therapy with protease inhibitors (relative risk, 0.84; P=0.19).

Confirmed cases of *P. carinii* pneumonia developed

TABLE 2. SUMMARY OF EVENTS ACCORDING TO TREATMENT GROUP.*

EVENT AND PCP PROPHYLAXIS GROUP†	ATOVAQUONE (N=536)		DAPSONE (N=521)		RR (95% CI)	P VALUE
	NO. OF PATIENTS WITH EVENT	EVENT RATE	NO. OF PATIENTS WITH EVENT	EVENT RATE		
	PCP‡					
All patients	122	15.7	135	18.4	0.85 (0.67–1.09)	0.20
Primary	67	11.3	81	14.1	0.81 (0.58–1.12)	0.20
Secondary	55	29.7	54	33.9	0.92 (0.62–1.34)	0.65
Death						
All patients	232	26.2	208	24.1	1.07 (0.89–1.30)	0.45
Primary	150	23.2	121	18.6	1.25 (0.98–1.59)	0.07
Secondary	82	34.2	87	41.2	0.85 (0.62–1.14)	0.28

*Rates are per 100 person-years. Relative risks for atovaquone versus dapsone and associated P values are derived from proportional-hazards regression models, with stratification factors corresponding to trial group (ACTG or CPCRA) and presence or absence of a history of *P. carinii* pneumonia at base line. PCP denotes *P. carinii* pneumonia, RR relative risk, and CI confidence interval.

†Patients with no history of *P. carinii* pneumonia received primary prophylaxis, and those with a history of *P. carinii* pneumonia received secondary prophylaxis.

‡A PCP event was defined as the first occurrence of confirmed or probable *P. carinii* pneumonia after randomization.

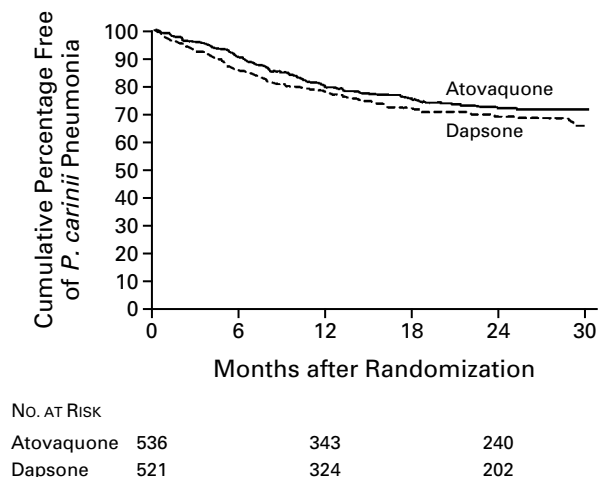


Figure 1. Kaplan–Meier Estimates of the Percentage of Patients Who Remained Free of *P. carinii* Pneumonia, According to Treatment Group.

in 93 patients assigned to atovaquone (11.6 cases per 100 person-years) and 109 patients assigned to dapsone (14.4 per 100 person-years; relative risk, 0.79; 95 percent confidence interval, 0.60 to 1.04; $P=0.09$).

Among patients who were receiving their originally assigned treatment or who had discontinued or switched treatment not more than 30 days previously (on-treatment analysis), *P. carinii* pneumonia developed in 83 patients assigned to atovaquone (17.0 cases per 100 person-years) and in 101 patients assigned to dapsone (20.8 per 100 person-years; relative risk, 0.80; 95 percent confidence interval, 0.59 to 1.07; $P=0.13$). Patients who discontinued all study treatment had a 37 percent lower rate of *P. carinii* pneumonia than those who continued to receive the study-supplied medication ($P=0.02$).

Toxoplasmosis

Confirmed or probable toxoplasmosis developed in 7 of the 170 patients who were seropositive for toxoplasma at base line (4 assigned to atovaquone and 3 assigned to dapsone) (relative risk, 1.18; 95 percent confidence interval, 0.26 to 5.30; $P=0.83$).

Mortality

A total of 440 patients died during the study. Death rates were similar for the two treatment groups; there were 232 deaths (26.2 per 100 person-years) among patients assigned to atovaquone and 208 (24.1 per 100 person-years) among those assigned to dapsone (relative risk, 1.07; 95 percent confidence interval, 0.89 to 1.30; $P=0.45$) (Table 2).

P. carinii Pneumonia or Death

A total of 555 patients had confirmed or probable *P. carinii* pneumonia or died: 281 assigned to atova-

quone (36.1 events per 100 person-years) and 274 assigned to dapsone (37.0 per 100 person-years; relative risk, 0.98; 95 percent confidence interval, 0.83 to 1.16; $P=0.80$).

Subgroup Analyses

Among patients receiving primary prophylaxis, the relative risk of *P. carinii* pneumonia for atovaquone versus dapsone was 0.81 ($P=0.20$), and the relative risk of death was 1.25 ($P=0.07$). Among patients receiving secondary prophylaxis, the relative risk was 0.92 ($P=0.65$) for *P. carinii* pneumonia and 0.85 ($P=0.28$) for death (Table 2). The relative risk of death was significantly different in the subgroup of patients receiving primary prophylaxis and the subgroup receiving secondary prophylaxis ($P=0.03$). The relative risk of *P. carinii* pneumonia in the atovaquone group versus the dapsone group was 0.99 among patients already receiving dapsone at base line ($P=0.95$) and 0.68 among those not receiving dapsone at base line ($P=0.05$).

Adverse Events and Discontinuation of Study Drugs

Among the patients assigned to atovaquone, 436 (81 percent) discontinued the study medication, including 146 who were switched to dapsone. The most common reasons for discontinuation were intolerance (25 percent), the patient's request (18 percent), development of *P. carinii* pneumonia (16 percent), and death (14 percent). Among the patients assigned to dapsone, 407 (78 percent) discontinued the medication, including 149 who were switched to atovaquone. For these patients, the most common reasons for discontinuation were intolerance (26 percent), development of *P. carinii* pneumonia (17 percent), death (17 percent), and the patient's request (9 percent).

The overall rates of discontinuation because of an inability to tolerate the study drug did not differ significantly between treatment groups (relative risk for atovaquone vs. dapsone, 0.94; $P=0.59$) (Table 3). Among patients who discontinued atovaquone because of intolerance, 74 percent had grade 1 or 2 adverse events, and 25 percent had grade 3 or 4 adverse events. In the dapsone group, 63 percent of the patients who discontinued the drug because of intolerance had grade 1 or 2 adverse events, and 36 percent had grade 3 or 4 adverse events. (Grades were not available for three patients.) The specific adverse events varied according to the treatment group. As compared with patients assigned to dapsone, more patients assigned to atovaquone discontinued the drug because of upper gastrointestinal symptoms (relative risk, 6.79; $P<0.001$) or diarrhea (relative risk, 16.6; $P=0.01$). However, fewer patients assigned to atovaquone discontinued the study drug because of hypersensitivity reactions, such as rash, fever, allergic reaction, pruritus, and dermatitis (relative risk, 0.50;

TABLE 3. DISCONTINUATION OF ORIGINALLY ASSIGNED STUDY DRUG ACCORDING TO BASE-LINE DAPSONE USE.*

REASON FOR DISCONTINUATION	ALL PATIENTS (N=1057)				BASE-LINE DAPSONE (N=546)				NO BASE-LINE DAPSONE (N=511)			
	ATOVA- QUONE (N=536)	DAPSONE (N=521)	RR (95% CI)	P VALUE	ATOVA- QUONE (N=285)	DAPSONE (N=261)	RR (95% CI)	P VALUE	ATOVA- QUONE (N=251)	DAPSONE (N=260)	RR (95% CI)	P VALUE
	no. of events (rate)				no. of events (rate)				no. of events (rate)			
Adverse event	133 (28.1)	137 (28.6)	0.94 (0.74–1.19)	0.59	80 (32.1)	24 (8.4)	3.78 (2.37–6.01)	<0.001	53 (23.6)	113 (58.4)	0.42 (0.30–0.58)	<0.001
Hyper-sensitivity	46 (9.7)	86 (18.0)	0.50 (0.35–0.72)	<0.001	23 (9.2)	11 (3.9)	2.28 (1.11–4.70)	0.03	23 (10.2)	75 (38.7)	0.29 (0.18–0.46)	<0.001
Anemia	0 (0.0)	10 (2.1)	—	0.001	0 (0.0)	5 (1.8)	—	0.02	0 (0.0)	5 (2.6)	—	0.06
Upper gastro-intestinal symptoms	34 (7.2)	5 (1.0)	6.79 (2.65–17.4)	<0.001	23 (9.2)	0 (0.0)	—	<0.001	11 (4.9)	5 (2.6)	1.87 (0.65–5.40)	0.25
Diarrhea	16 (3.4)	1 (0.2)	16.6 (2.20–125)	0.01	10 (4.0)	0 (0.0)	—	0.002	6 (2.7)	1 (0.5)	5.76 (0.69–48.3)	0.11
Patient's request	95 (20.1)	45 (9.4)	2.06 (1.44–2.94)	<0.001	50 (20.1)	26 (9.1)	2.13 (1.32–3.43)	0.002	45 (20.1)	19 (9.8)	2.09 (1.21–3.59)	0.01
Adverse event or patient's request	228 (48.1)	182 (38.0)	1.21 (1.00–1.48)	0.05	130 (52.2)	50 (17.5)	2.90 (2.09–4.04)	<0.001	98 (43.7)	132 (68.2)	0.66 (0.51–0.86)	0.002

*Relative risks (RR) for atovaquone versus dapson and associated P values and 95 percent confidence intervals (CI) are derived from a Cox proportional-hazards regression model with stratification factors corresponding to research organization (CPCRA or ACTG), presence or absence of a history of *P. carinii* pneumonia, and toxoplasmosis titer at base line. Rates are per 100 person-years. For comparisons with no events in one treatment group, P values were calculated with Fisher's exact test.

P<0.001), or anemia (0 vs. 2.1 per 100 person-years; P=0.001).

Of the patients receiving dapson at base line, those who were assigned to atovaquone were significantly more likely than those assigned to dapson to discontinue the assigned treatment because of adverse events (relative risk, 3.78; 95 percent confidence interval, 2.37 to 6.01; P<0.001) (Table 3). The opposite was true for patients who were not taking dapson at base line (relative risk, 0.42; 95 percent confidence interval, 0.30 to 0.58; P<0.001). The difference in relative risks was largely the result of different rates of discontinuation among patients assigned to dapson. There was a sixfold difference in the rate of discontinuation of study-assigned dapson because of adverse events between those taking and those not taking dapson at base line (8.4 and 58.4 per 100 person-years, respectively). Table 3 shows the rates of discontinuation due to the most commonly reported adverse events, according to dapson use at base line.

A significantly larger number of patients assigned to atovaquone requested that the study medication be discontinued in the absence of an adverse event or *P. carinii* pneumonia (Table 3). However, the proportion of patients who discontinued the study drug either at their own request or because of intolerance did not differ significantly between the atovaquone and dapson groups (relative risk, 1.21; P=0.05). The risk of discontinuation for either of these reasons

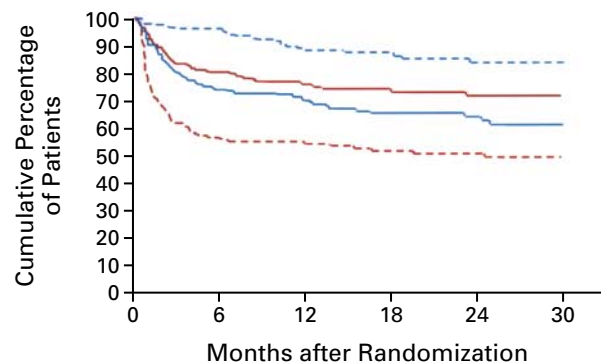


Figure 2. Kaplan–Meier Estimates of the Percentage of Patients Who Continued to Take the Assigned Study Drug without the Development of Intolerance.

Blue lines represent patients receiving dapson at base line, red lines patients not receiving dapson at base line, solid lines patients assigned to atovaquone, and dashed lines patients assigned to dapson.

was significantly influenced by base-line use of dapson (Table 3).

The median time during which patients received the study medication was similar in the two treatment groups but differed significantly according to dapson use at base line (Fig. 2). The median time that patients continued to use assigned dapson was 10.9 months for those who were receiving dapson at base line and 3.9 months for those who were not (P<0.001). The

median time that patients continued to use atovaquone was similar in these two subgroups: 7.0 months for those who were receiving dapsone at base line and 7.4 months for those who were not.

DISCUSSION

In patients with HIV infection, the use of trimethoprim-sulfamethoxazole as prophylactic treatment has been limited by adverse events.^{6,7} Various regimens for desensitization to trimethoprim-sulfamethoxazole have been recommended,¹¹ and dose escalation has been attempted.^{12,13} These strategies may be inadvisable or unsuccessful in some patients, necessitating the use of alternative agents, including dapsone, dapsone plus pyrimethamine, and aerosolized pentamidine.¹⁴ In this study, atovaquone suspension and dapsone at a 100-mg daily dose were similarly effective for the prevention of *P. carinii* pneumonia among patients who could not tolerate trimethoprim-sulfamethoxazole. This finding was consistent for both patients who were receiving primary prophylaxis and those who were receiving secondary prophylaxis and for both patients who were receiving dapsone at base line and those who were not.

The efficacy of dapsone as prophylaxis against *P. carinii* pneumonia has been evaluated in several studies that used various doses of dapsone, with or without pyrimethamine.^{6,7} With the exception of one small study, none of these studies were specifically designed to enroll patients who could not tolerate trimethoprim-sulfamethoxazole.¹⁵

A potential advantage of atovaquone for the prevention of *P. carinii* pneumonia is its antitoxoplasma activity.¹⁴ Although we found that atovaquone and dapsone had similar efficacy for the prevention of *P. carinii* pneumonia, we were unable to evaluate the efficacy of atovaquone for the prevention of toxoplasmosis because of the low seroprevalence of toxoplasma among the study participants and the occurrence of very few cases of toxoplasmosis.

The rates of *P. carinii* pneumonia decreased with increasing duration of follow-up in both treatment groups, perhaps as a result of the introduction of more potent antiretroviral therapies during the course of the study. (Seventy-two percent of the participants at two years of follow-up were receiving regimens containing protease inhibitors.) There was also a substantial decline in the rates of HIV-related opportunistic events during this time.^{16,17} On the other hand, it is not clear why there was a greater decline in the rate of *P. carinii* pneumonia among the patients who discontinued the study medications than among those who continued to receive them. The regimens used as prophylaxis against *P. carinii* pneumonia (largely aerosolized pentamidine and dapsone) by patients who discontinued the assigned treatment are unlikely to explain the lower rate of *P. carinii* pneumonia. It is also unlikely that patients who dis-

continued the study medications were those with a more favorable response to antiretroviral therapy and a lower risk of *P. carinii* pneumonia. It is possible that those who discontinued treatment and became lost to follow-up (about 6 percent of the patients) had a higher rate of *P. carinii* pneumonia. The similar rate of loss to follow-up in the two treatment groups reduces the likelihood of a bias in the treatment effects.

A substantial proportion of participants had adverse events that necessitated discontinuation of the study drugs. Overall, there was no significant difference between the atovaquone and dapsone groups in the rate of adverse events or in the median time during which patients received the assigned treatment. However, dapsone use before randomization was an important determinant of the relative tolerance of these two regimens. Patients who were receiving dapsone at base line were randomly assigned to either the continued use of dapsone or the initiation of atovaquone. Because few patients were receiving atovaquone before randomization, a comparable group of patients receiving atovaquone at base line could not be studied. Patients who were receiving dapsone at base line were more likely to tolerate the continued use of dapsone than the initiation of atovaquone. The opposite was true for those not receiving dapsone at base line: they tolerated atovaquone better than dapsone. The results for the patients in the latter group, who did not already have a demonstrated tolerance of dapsone, may be more applicable to patients who cannot tolerate trimethoprim-sulfamethoxazole and who are therefore newly eligible for alternative prophylactic regimens.

Each treatment was associated with distinct patterns of adverse events. With atovaquone, there were significantly higher rates of upper gastrointestinal symptoms and diarrhea among the patients who were receiving dapsone at base line. With dapsone, hypersensitivity reactions and anemia predominated.

Survival rates were similar whether patients were assigned to atovaquone or to dapsone. A previous study reported higher mortality among patients receiving dapsone than among those receiving aerosolized pentamidine for secondary prophylaxis against *P. carinii* pneumonia.¹⁸ However, this result was not confirmed in our study or in a recent meta-analysis.¹⁹

In conclusion, this large randomized study compared atovaquone with the most widely used alternative, dapsone, as prophylaxis against *P. carinii* pneumonia in HIV-infected patients with a history of intolerance of trimethoprim-sulfamethoxazole. The rates of *P. carinii* pneumonia, survival, and tolerance were similar in the atovaquone and dapsone groups. However, among patients who were not receiving dapsone at base line, atovaquone was better tolerated, and it may be the preferred therapy for such patients. Patients who were already receiving dapsone

tolerated it better than atovaquone, a result indicating that such patients should continue to take dapsone. The high rates of *P. carinii* pneumonia and intolerance with both medications suggest that further research is needed to find better options for prophylaxis against *P. carinii* pneumonia among patients who cannot tolerate trimethoprim-sulfamethoxazole.

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APPENDIX

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