

Trimethoprim–Sulfamethoxazole Compared with Ciprofloxacin for Treatment and Prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* Infection in HIV-Infected Patients

A Randomized, Controlled Trial

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Background: In developing countries, *Isospora belli* and *Cyclospora cayetanensis* frequently cause chronic diarrhea in HIV-infected patients.

Objective: To compare 1 week of trimethoprim–sulfamethoxazole treatment and 1 week of ciprofloxacin treatment in HIV-infected patients with chronic diarrhea caused by *I. belli* and *C. cayetanensis*.

Design: Randomized, controlled trial.

Setting: HIV clinic in Port-au-Prince, Haiti.

Patients: 42 HIV-infected patients with chronic diarrhea due to *I. belli* ($n = 22$) or *C. cayetanensis* ($n = 20$).

Interventions: Patients were randomly assigned to receive oral trimethoprim–sulfamethoxazole (160 mg or 800 mg) or ciprofloxacin (500 mg) twice daily for 7 days. Patients who responded clinically and microbiologically received prophylaxis for 10 weeks (1 tablet orally, three times per week).

Measurements: Treatment success was measured by cessation of diarrhea and negative stool examination at day 7. Prophylaxis success was measured by recurrent disease rate.

Results: Diarrhea ceased in all 19 patients treated with trimethoprim–sulfamethoxazole. Eighteen of 19 patients had negative results on stool examination at day 7 (95%). Among the 23 patients who received ciprofloxacin, diarrhea ceased in 20 (87% [CI, 66% to 97%]) and 16 had negative results on stool examination at day 7 (70%). By survival analysis, diarrhea from isosporiasis and cyclosporiasis ceased more rapidly with trimethoprim–sulfamethoxazole than with ciprofloxacin. All patients receiving secondary prophylaxis with trimethoprim–sulfamethoxazole remained disease-free, and 15 of 16 patients receiving secondary prophylaxis with ciprofloxacin remained disease-free.

Conclusions: A 1-week course of trimethoprim–sulfamethoxazole is effective in HIV-infected patients with cyclosporiasis or isosporiasis. Although ciprofloxacin is not as effective, it is acceptable for patients who cannot tolerate trimethoprim–sulfamethoxazole.

Ann Intern Med. 2000;132:885-888.

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Diarrhea is one of the most common clinical manifestations of HIV infection (1–4). In developing countries, *Cryptosporidium parvum*, *Isospora belli*, and *Cyclospora cayetanensis* are the most prevalent pathogens associated with chronic diarrhea in HIV-infected persons (4).

Isosporiasis and cyclosporiasis respond well to a 10-day course of trimethoprim–sulfamethoxazole given orally four times per day (5, 6). The median time to cessation of diarrhea after commencement of treatment is 2 days. The rapid clinical response of *I. belli* and *C. cayetanensis* suggests that a reduced dose could be effective (5–7). Trimethoprim–sulfamethoxazole (twice daily for 7 days) was effective for treatment of chronic diarrhea due to *C. cayetanensis* in patients who were presumed to be HIV-negative (8). We evaluated the response of HIV-infected patients with cyclosporiasis and isosporiasis to 1 week of treatment with twice-daily trimethoprim–sulfamethoxazole.

Our second objective was to evaluate the effectiveness of ciprofloxacin in the treatment and secondary prophylaxis of cyclosporiasis and isosporiasis in HIV-infected patients. Although trimethoprim–sulfamethoxazole is highly effective for the treatment of isosporiasis and cyclosporiasis, long-term secondary prophylaxis is necessary to prevent recurrence, which occurs in approximately 50% of patients (5–7). Side effects of trimethoprim–sulfamethoxazole are not uncommon (9, 10). Therefore, an effective sulfa-free alternative is needed for treatment and prophylaxis of cyclosporiasis and isosporiasis. In vitro and in vivo studies suggest that quinolones may be active against *Coccidia* species (11–13).

Methods

Our study was conducted at the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) clinic in Port-au-Prince, Haiti, from January 1997 to August 1998. The clinic is the national HIV testing center in Haiti. All HIV-positive patients who report chronic diarrhea are referred to a physician for evaluation.

We selected ambulatory patients who were 18 to 60 years of age, lived within 30 km of the clinic, had chronic diarrhea (≥ 1 episode per month), had two liquid stool specimens that took the shape of the container, and had *I. belli* or *C. cayetanensis* identified on two occasions within 10 days before initiation of therapy. We excluded pregnant women, persons who had received ciprofloxacin or trimethoprim–sulfamethoxazole within 2 weeks of enrollment, and patients with other enteric pathogens.

Stool specimens were mixed with two drops of

saline and examined microscopically for ova and helminths. Coccidial oocysts were identified in saline wet mounts, and positive slides were stained for confirmation by a variation of the modified Kinyoun acid-fast method. The criterion used for identification of *I. belli* was the presence of large, oval, acid-fast oocysts (20 to 30 μm by 10 to 19 μm) that contained two sporoblasts. The criterion used for identification of *Cyclospora* species was the presence of round acid-fast oocysts that were intermediate in size (8 to 9 μm) between *Cryptosporidium* and *Isopora* species.

Patients were randomly assigned to receive ciprofloxacin (500 mg) or trimethoprim-sulfamethoxazole (160 mg or 800 mg) orally twice per day for 1 week. Stool examination was repeated on days 3 and 7 of therapy. Weight, clinical signs of dehydration (dry mucous membranes, skin tenting, and orthostatic hypotension), and consistency and number of stools were recorded at each visit. Response to treatment was defined by clinical and laboratory criteria. Clinical response was defined as cessation of diarrhea as reported by the patient and the provision of a stool specimen that did not conform to the shape of the container. Microbiological response was defined as a stool examination that was negative for *C. cayetanensis* and *I. belli* at day 7. Patients who responded clinically and microbiologically were defined as having a complete response.

Patients who did not have complete response to 7 days of therapy were switched to standard therapy: trimethoprim-sulfamethoxazole given orally four times per day (5, 6). Patients with a complete response to 7 days of therapy continued to receive the same drug at a reduced dose for secondary prophylaxis with ciprofloxacin (500 mg) or trimethoprim-sulfamethoxazole (160 mg or 800 mg). Oral prophylaxis was given three times per week for 10 weeks. During this period, patients underwent a weekly stool examination. Prophylaxis was considered to have failed in patients who had recurrent diarrhea and *C. cayetanensis* or *I. belli* in their stools. Such patients were treated again with the standard 10-day regimen of trimethoprim-sulfamethoxazole (5, 6).

Exact CIs for treatment outcomes were based on the binomial distribution. Time until cessation of diarrhea in the two treatment groups was compared by using the log-rank test. Survival analysis was done by using the Kaplan-Meier method.

The study protocol and consent process were approved by the Human Rights Committees of GHESKIO and Cornell University Medical College, New York, New York. All patients provided informed consent.

Results

Between January 1997 and August 1998, 6415 persons presented to GHESKIO for voluntary HIV testing and 2373 persons (37%) were found to be HIV-positive. Of the HIV-infected persons, 407 (17%) reported chronic diarrhea and were referred for further evaluation.

Of the HIV-infected patients evaluated for chronic diarrhea, 252 were able to provide two stool specimens for laboratory evaluation. Among these 252 patients, 29 (12%) were infected with *I. belli* and 35 (14%) were infected with *C. cayetanensis*. No patient was infected with both organisms. Participants with isosporiasis were clinically indistinguishable from those with cyclosporiasis. Of the 29 patients infected with *I. belli*, 22 (76%) met entry criteria and were enrolled in the study. Of the 35 patients infected with *C. cayetanensis*, 20 (57%) were enrolled.

The median age of the 42 study patients was 29 years; 57% of patients were male. The median duration of diarrhea was 4.3 months, and 40% of patients lost more than 10% of body weight. Forty percent of patients had a prior AIDS-defining illness. These variables did not significantly differ between patients with isosporiasis and those with cyclosporiasis or between the treatment groups. No patients were taking other medications at the time of this study, including antiretroviral medications, which are not the standard of care in Haiti.

Isosporiasis

Of the 22 patients with isosporiasis, 10 were randomly assigned to receive trimethoprim-sulfamethoxazole and 12 were randomly assigned to receive ciprofloxacin. At enrollment, the two treatment groups did not differ significantly with respect to duration of diarrhea, weight loss, or history of other AIDS-defining illnesses. Results of treatment are shown in the **Table**. According to survival analysis, patients treated with trimethoprim-sulfamethoxazole had a more rapid clinical response than patients treated with ciprofloxacin (**Figure**). After initiation of therapy, diarrhea ceased in all patients receiving trimethoprim-sulfamethoxazole within a median of 2 days and in 10 of 12 patients receiving ciprofloxacin within a median of 4.5 days ($P = 0.022$). One patient who received trimethoprim-sulfamethoxazole had persistence of *I. belli* in the absence of diarrhea and was successfully treated with trimethoprim-sulfamethoxazole for 3 additional days. Three of 12 patients in the ciprofloxacin group had persistence of fecal *I. belli* (25%); 2 of these 3 had associated diarrhea. All 3 patients were successfully treated with trimethoprim-sulfamethoxazole. Patients with complete response to 7 days of therapy received secondary prophylaxis with trimethoprim-

Table. Response to 1 Week of Treatment with Trimethoprim–Sulfamethoxazole or Ciprofloxacin*

Response	Patients Infected with <i>Iso spor a belli</i> [95% CI]		Patients Infected with <i>Cyclo spor a cayetanensis</i> [95% CI]		All Patients [95% CI]	
	Trimethoprim–Sulfamethoxazole Group (n = 10)	Ciprofloxacin Group (n = 12)	Trimethoprim–Sulfamethoxazole Group (n = 9)	Ciprofloxacin Group (n = 11)	Trimethoprim–Sulfamethoxazole Group (n = 19)	Ciprofloxacin Group (n = 23)
	← n (%) →					
Cessation of diarrhea by day 7	10 (100 [69–100])	10 (83 [52–98])	9 (100 [66–100])	10 (90 [59–100])	19 (100 [82–100])	20 (87 [66–97])
Negative results on stool examination at day 7	9 (90 [55–100])	9 (75 [43–95])	9 (100 [66–100])	7 (64 [31–89])	18 (95 [74–100])	16 (69 [47–87])

* No significant difference was seen in the proportion of patients who responded to 1 week of treatment with trimethoprim–sulfamethoxazole and those who responded to 1 week of treatment with ciprofloxacin (Fisher exact test).

sulfamethoxazole or ciprofloxacin for 10 weeks. No recurrences were observed during the 10-week period. No patients receiving trimethoprim–sulfamethoxazole or ciprofloxacin discontinued therapy with the drug because of side effects.

Cyclosporiasis

Of the 20 patients with cyclosporiasis, 9 were randomly assigned to receive trimethoprim–sulfamethoxazole and 11 were randomly assigned to receive ciprofloxacin. At enrollment, the two groups did not differ significantly with respect to duration of diarrhea, history of weight loss, or history of other AIDS-defining illnesses. According to survival analysis, patients treated with trimethoprim–sulfamethoxazole had a more rapid clinical response than patients treated with ciprofloxacin (Figure). After initiation of therapy, diarrhea ceased in all patients receiving trimethoprim–sulfamethoxazole (median time to cessation, 3.0 days) and in 10 of 11 patients receiving ciprofloxacin (median time to cessation, 4.0 days) ($P = 0.047$). At the end of 7 days, all patients receiving trimethoprim–sulfamethoxazole had negative results on stool examination. Four patients treated with ciprofloxacin had persistence of fecal *C. cayetanensis*; 1 of these 4 had continuing diarrhea. All 4 patients were successfully treated with trimethoprim–sulfamethoxazole. Patients with a complete response to 7 days of therapy received secondary prophylaxis with trimethoprim–sulfamethoxazole or ciprofloxacin for 10 weeks. No recurrences were observed in the trimethoprim–sulfamethoxazole group, but 1 of 7 patients receiving ciprofloxacin had a recurrence after 4 weeks. No patients receiving trimethoprim–sulfamethoxazole or ciprofloxacin discontinued therapy with the drug because of side effects.

Discussion

Chronic diarrhea is one of the most common clinical manifestations of HIV infection in developing countries and is a major cause of illness and

death (4, 14). More than 90% of HIV-infected patients develop chronic diarrhea (14). In our study, 25% of the HIV-positive patients evaluated for chronic diarrhea were infected with *I. belli* or *C. cayetanensis*. Trimethoprim–sulfamethoxazole, four times per day for 10 days, is currently recommended for HIV-infected persons with chronic diarrhea caused by *I. belli* or *C. cayetanensis*. However, because trimethoprim–sulfamethoxazole causes side effects in HIV-infected persons, a lower dose or an alternate drug must be used (10).

We report that a 7-day regimen of trimethoprim–sulfamethoxazole given twice daily is effective in HIV-infected patients with isosporiasis or cyclosporiasis. Diarrhea ceased in all patients treated with this reduced dose of trimethoprim–sulfamethoxazole; only one patient had persistence of organisms in the stool after therapy. These results are similar

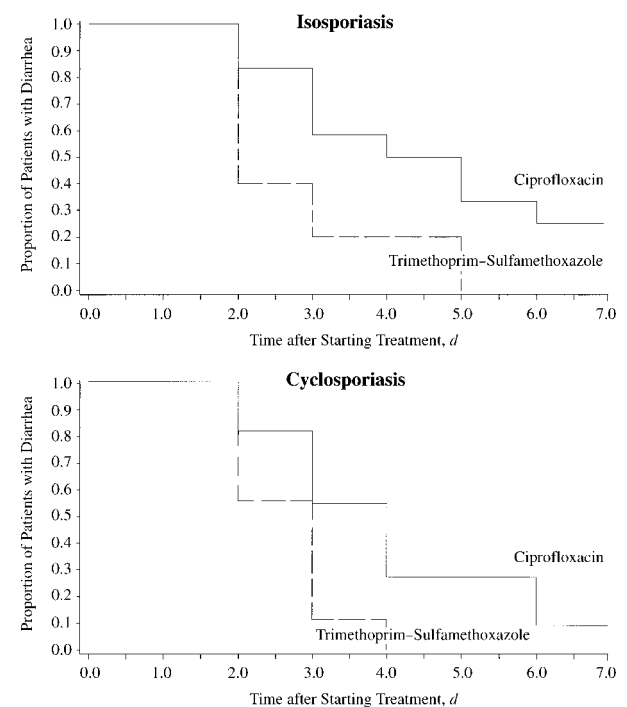


Figure. Kaplan–Meier estimate of patients with isosporiasis and cyclosporiasis who were free of diarrhea after starting treatment with trimethoprim–sulfamethoxazole or ciprofloxacin.

to those found with 7-day trimethoprim-sulfamethoxazole treatment of cyclosporiasis in persons who were presumed to be HIV-negative (8). Secondary prophylaxis with trimethoprim-sulfamethoxazole successfully prevented recurrence of both isosporiasis and cyclosporiasis.

Our study shows that ciprofloxacin is an effective alternative for the treatment and prophylaxis of isosporiasis and cyclosporiasis. Of the patients treated with ciprofloxacin, 87% (95% CI, 66% to 97%) had cessation of diarrhea within 7 days of starting treatment and 69% (CI, 47% to 87%) had no organisms present in the stool after 7 days. More than 90% of patients who received ciprofloxacin prophylaxis remained disease- and organism-free. In our previous experience in Haiti (5-7), we found that HIV-infected persons with isosporiasis and cyclosporiasis rarely clear the organisms from their stool without effective therapy.

We conclude that HIV-infected patients with isosporiasis or cyclosporiasis respond well to a 1-week course of trimethoprim-sulfamethoxazole. Although ciprofloxacin is not as effective, it is an acceptable alternative in patients who cannot tolerate trimethoprim-sulfamethoxazole.

From Cornell University Medical College, New York, New York, and Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti.

Grant Support: In part by the U.S. Public Health Service (R37 AI22624, TW 00018, T32 AI07613, K01 TW00002).

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