



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/28/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

## Isosporiasis (Cystoisosporiasis) (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Antiretroviral treatment of HIV-infected children to reverse or prevent severe immunodeficiency may reduce the incidence or prevent recurrence of isosporiasis (**CIII**).
- Careful hand washing and thorough washing of fruits and vegetables are recommended to prevent exposure (**AIII**).
- Travelers to endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables, all of which can be contaminated (**BIII**).
- Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in HIV-infected children (**AI\***).
- In those with severe immunosuppression, treatment should be followed by secondary prophylaxis with TMP-SMX until severe immunosuppression resolves (**AII\***).
- As with all causes of diarrhea, supportive care, including replenishment of fluids and electrolytes, is essential (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Epidemiology

*Isospora belli* (*Cystoisospora belli*) is an intestinal coccidian parasite in the phylum *Apicomplexa*. It was first linked with human disease in 1915 and is believed to infect only humans.<sup>1</sup> Isosporiasis, also known as cystoisosporiasis, occurs worldwide but is more prevalent in tropical and subtropical regions; it has been reported as an etiologic agent of traveler's diarrhea.<sup>2-4</sup> Prior to the availability of combination antiretroviral therapy (cART), the prevalence of isosporiasis among adults with AIDS was reported to be 15% in Haiti but <0.2% in the United States.<sup>1,5</sup>

Infected individuals pass non-infective, unsporulated (immature) oocysts in their stools. The oocysts must sporulate (mature) outside the host, in favorable environmental conditions, to become infective.<sup>1,4</sup> Therefore, direct person-to-person transmission is unlikely. Infection results from ingestion of sporulated oocysts, such as in contaminated food or water. In the proximal small intestine, the ingested oocysts release sporozoites that invade the intestinal epithelial cells. They then enter an asexual reproduction stage that infects neighboring epithelial cells. Sexual gametocytes are also produced; their fertilization results in unsporulated oocysts, which are shed in stool.<sup>1,6</sup>

## Clinical Manifestations

On the basis of limited data, the incubation period averages approximately 1 week but may range from several days to 2 or more weeks; symptom onset may be acute or insidious.<sup>1,2,4,5</sup> The most common symptom is watery (non-bloody) diarrhea, which can be profuse and result in dehydration, weight loss, and malabsorption. Affected people also can have crampy abdominal pain, flatulence, nausea, vomiting, anorexia, and low-grade fever. Biliary disease (cholecystitis/choangiopathy) and reactive arthritis also have been reported.<sup>7,8</sup> Whereas immunocompetent hosts typically have self-limited infection, chronic, debilitating diarrhea is common in untreated HIV-infected patients.

## Diagnosis

Isosporiasis is diagnosed by identifying *I. belli* oocysts in stool (or duodenal aspirates using the Entero-Test) or developmental stages of the parasite in biopsy specimens (such as of the small intestine). The oocysts are relatively large (23–33 µm long by 10–19 µm wide) but may be difficult to find. Oocysts may be shed in low numbers even by individuals who have severe diarrhea, which underscores the utility of repeated stool examinations, using methods that concentrate and highlight the parasite. Although staining is frequently variable, the organism can be identified with use of a modified acid-fast stain, staining bright red on a green background.<sup>5,6</sup> The organism also autofluoresces when viewed by ultraviolet fluorescence microscopy.<sup>1</sup> Blunting and clubbing of villi and hypertrophied crypts can be seen on small bowel biopsy. There also may be an increase in lymphocytes, plasma cells, and eosinophils in the lamina propria.<sup>6</sup> Serologic tests for diagnosing *I. belli* infection are not available. Peripheral eosinophilia occurs in up to half of patients. Polymerase chain reaction is a promising diagnostic tool but is not yet commercially available.<sup>9</sup>

## Prevention Recommendations

### *Preventing Exposure*

Careful hand washing and thorough washing of fruits and vegetables are recommended (**AIII**). As always, travelers to endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables (**BIII**).

### *Preventing Disease*

There are no U.S. recommendations for primary prophylaxis of isosporiasis. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX, 160 mg and 800 mg, respectively) was effective in preventing isosporiasis in adults with World Health Organization stage 2 or 3 HIV infection in Cote d'Ivoire.<sup>10</sup> In addition, in an observational study, the incidence of isosporiasis decreased after widespread availability of cART, except among persons with CD4 counts less than 50 cells/µL.<sup>11</sup> Although there have been no studies in children, the relationship between severe immunosuppression and disease in adults suggests that initiation of cART in HIV-infected children before development of severe immunodeficiency may reduce the incidence or prevent recurrence of isosporiasis (**CIII**).

## Treatment Recommendations

### *Treating Disease*

TMP-SMX is the recommended treatment for isosporiasis. Three randomized trials performed in HIV-infected adults in Haiti not receiving antiretroviral therapy have demonstrated the effectiveness of various regimens.<sup>5,12,13</sup> In the first study, TMP-SMX (160 mg and 800 mg, respectively) was administered 4 times daily for 10 days and then twice daily for 3 weeks. Improvement in diarrheal symptoms occurred within a few days, but 7 of 15 patients (47%) had recurrent symptoms within a mean of 8 +/- 5.8 weeks following completion of therapy.<sup>5</sup> In the second study, TMP-SMX (160 mg and 800 mg, respectively) was administered 4 times daily for 10 days; subjects were then randomized to 1 of 3 secondary prophylaxis arms. At the completion of the initial 10 days of TMP-SMX, all 32 participants had resolution of diarrhea and abdominal pain as well as stool samples that tested negative for *I. belli*.<sup>12</sup> In the third study, subjects were randomized to receive either TMP-SMX (160 mg and 800 mg, respectively) or ciprofloxacin (500 mg) twice daily for 7 days. TMP-SMX treatment resulted in cessation of diarrhea in all 10 patients and negative results on stool examination at day 7 in 9 of the 10, while ciprofloxacin resulted in resolution of diarrhea in 10 of 12 patients and 9 of 12 with negative stool examinations.<sup>13</sup> On the basis of these studies in adults, the recommended treatment for HIV-infected children is TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days (**AI\***). If symptoms worsen or persist, the TMP-SMX dose may be increased to 5 mg/kg/dose of the trimethoprim component, 3 to 4 times daily, for 10 days or the duration of treatment lengthened (up to 3–4

weeks) **(CIII)**.<sup>5,14</sup> Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Daily pyrimethamine (50–75 mg in adults), with folinic acid (10–25 mg/day) to prevent myelosuppression, may be an effective therapy and is typically the alternative for patients who are intolerant of TMP-SMX **(BIII)**.<sup>15</sup> Other agents to consider in a TMP-SMX-intolerant patient include ciprofloxacin **(CI\*)** or nitazoxanide **(CIII)**. Based on the study previously cited,<sup>13</sup> ciprofloxacin is less effective than TMP-SMX, and nitazoxanide has only been studied in small numbers of HIV-uninfected children and adults.<sup>16</sup> As reviewed above, the relationship between the use of cART and recovery from isosporiasis remains unknown. However, because the incidence of isosporiasis has been reported to be higher in those with more severe immune suppression, it seems reasonable to initiate cART in children with isosporiasis not already receiving cART to prevent recurrence **(CIII)**.

As with all causes of diarrhea, supportive care, including replenishment of fluids and electrolytes, is essential **(AIII)**.

### ***Monitoring and Adverse Events (Including IRIS)***

Immune reconstitution inflammatory syndrome has not been reported in association with treatment of isosporiasis. In general, recommended treatment regimens are well tolerated.

### ***Managing Treatment Failure***

Reports of treatment failure are relatively uncommon. Mixed data regarding treatment outcomes are available for albendazole,<sup>17-19</sup> doxycycline,<sup>20</sup> roxithromycin,<sup>21</sup> and spiramycin.<sup>22</sup>

### ***Preventing Recurrence***

Following treatment of an acute episode, secondary prophylaxis should be continued in those with severe immunosuppression (Centers for Disease Control and Prevention [CDC] immunologic category 3) for an indefinite period until sustained immunologic recovery is observed **(AII\*)**. Pape et al., randomized HIV-infected adults completing therapy for acute infection to one of three regimens: TMP-SMX (160 mg and 800 mg, respectively) three times per week, sulfadoxine (500 mg) plus pyrimethamine (25 mg) once weekly, or placebo.<sup>12</sup> The two active treatment arms were equally effective in preventing relapse. However, the combination of sulfadoxine and pyrimethamine is not recommended in the United States because of increased risk of severe cutaneous reactions. In another study, adult patients with a clinical response following treatment of acute infection with TMP-SMX or ciprofloxacin received secondary prophylaxis for 10 weeks with the same agent as treatment, but at reduced doses: TMP-SMX (160 mg and 800 mg, respectively) or ciprofloxacin (500 mg) three times per week. The two agents were equally effective in preventing recurrence during the monitoring period.<sup>13</sup> Based on these findings in adults, acceptable regimens in HIV-infected children include TMP-SMX, 2.5 mg/kg body weight twice daily of the trimethoprim component, administered 3 days per week. The 3 days per week can be three consecutive days or an alternating-day schedule (e.g., Monday-Wednesday-Friday) **(AII\*)**. Patients intolerant of TMP-SMX may receive pyrimethamine (plus folinic acid) as secondary prophylaxis<sup>15</sup> **(BIII)**. Ciprofloxacin three times weekly can be considered as a second-line alternative **(CI\*)**.<sup>22</sup>

### ***Discontinuing Secondary Prophylaxis***

There are no data to provide guidance regarding the duration of secondary prophylaxis. All patients should be monitored for recurrence **(BIII)** and those with severe immunosuppression may require secondary prophylaxis indefinitely **(CIII)**. Secondary prophylaxis can probably be discontinued in patients who demonstrate sustained recovery from severe immunosuppression. In adults, a CD4 count >200 cells/ $\mu$ L for at least 6 months is recommended to discontinue secondary prophylaxis. In children, a reasonable time to discontinue secondary prophylaxis would be after sustained improvement in CD4 count or CD4 percentage from CDC immunologic category 3 to 1 or 2.

## References

1. Lindsay DS, Dubey JP, Blagburn BL. Biology of *Isospora* spp. from humans, nonhuman primates, and domestic animals. *Clin Microbiol Rev*. Jan 1997;10(1):19-34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8993857>.
2. Shaffer N, Moore L. Chronic travelers' diarrhea in a normal host due to *Isospora belli*. *J Infect Dis*. Mar 1989;159(3):596-597. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2915177>.
3. Godiwala T, Yaeger R. *Isospora* and traveler's diarrhea. *Ann Intern Med*. Jun 1987;106(6):908-909. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3579077>.
4. Wittner M, Tanowitz HB, Weiss LM. Parasitic infections in AIDS patients. Cryptosporidiosis, isosporiasis, microsporidiosis, cyclosporiasis. *Infect Dis Clin North Am*. Sep 1993;7(3):569-586. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8254160>.
5. DeHovitz JA, Pape JW, Boncy M, Johnson WD, Jr. Clinical manifestations and therapy of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Jul 10 1986;315(2):87-90. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3487730>.
6. Pape JW, Johnson WD, Jr. *Isospora belli* infections. *Prog Clin Parasitol*. 1991;2:119-127. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1893117>.
7. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: Nitazoxanide treatment failure in chronic isosporiasis. *Am J Trop Med Hyg*. Aug 2001;65(2):94-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11508398>.
8. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM JR, Torre-Cisneros J. *Isospora belli* reactive arthritis in a patient with AIDS [Letter]. *Ann Rheum Di*. 1994;53:618-9. Available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1005417/>.
9. ten Hove RJ, van Lieshout L, Brienen EA, Perez MA, Verweij JJ. Real-time polymerase chain reaction for detection of *Isospora belli* in stool samples. *Diagn Microbiol Infect Dis*. Jul 2008;61(3):280-283. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18424043>.
10. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. May 1 1999;353(9163):1463-1468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10232311>.
11. Guiguet M, Furco A, Tattevin P, Costagliola D MJ-M. HIV-associated *Isospora belli* infection: incidence and risk factors in the French Hospital Database on HIV. *HIV Medicine* 2007;8:124-30. 2007. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17352769>
12. Pape JW, Verdier RI, Johnson WD, Jr. Treatment and prophylaxis of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. Apr 20 1989;320(16):1044-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2927483>.
13. Verdier RI, Fitzgerald DW, Johnson WD, Jr., Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients. A randomized, controlled trial. *Ann Intern Med*. Jun 6 2000;132(11):885-888. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10836915>.
14. Whiteside ME, Barkin JS, May RG, et al. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. 1984;33(6):1065-1072. Available at [http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=6334448&ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=6334448&ordinalpos=16&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum).
15. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. *Isospora belli* infection: treatment with pyrimethamine. *Ann Intern Med*. Sep 15, 1988;109(6):474-475. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3261956>.
16. Romero Cabello R, Guerrero LR, Munoz Garcia MR, Geyne Cruz A. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg*. Nov-Dec 1997;91(6):701-703. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9580117>.
17. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scand J Infect Dis*. 2002;34:859-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12578164>
18. Dionisio D, Sterrantino G, Meli M, Leoncini F, Orsi A, Nicoletti P. Treatment of isosporiasis with combined

albendazole and ornidazole in patients with AIDS. *AIDS*. Sep 1996;10(11):1301-1302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8883600>.

19. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Aliment Pharmacol Ther*. 2002; 16(3):595-601. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11876715](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11876715).
20. Meyohas MC, Capella F, Poirot JL LI, Binet D, Eliaszewicz M, Frottier J. Treatment with doxycycline and nifuroxazide of *Isospora belli* infection in AIDS. *Pathol Biol (Paris)*. 1990;38:589-91. 1990. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2385457>
21. Musey KL, Chidiac C, Beaucaire G, Houriez S, Fourrier A. Effectiveness of roxithromycin for treating *Isospora belli* infection. *J Infect Dis*. Sep 1988;158(3):646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3411149>.
22. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to *Isospora belli* with spiramycin: a case report. *J Infect Dis*. Dec 1985;152(6):1336-1338. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4067332>.

### Dosing Recommendations for Prevention and Treatment of Isosporiasis (Cystoisosporiasis)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b>	There are no U.S. recommendations for primary prophylaxis of isosporiasis.	N/A	Initiation of cART to avoid advanced immunodeficiency may reduce incidence; TMP-SMX prophylaxis may reduce incidence.
<b>Secondary Prophylaxis</b>	<p><u>If Severe Immunosuppression:</u></p> <ul style="list-style-type: none"> <li>• Administer TMP-SMX 2.5 mg/kg body weight of TMP component twice daily by mouth 3 times per week</li> </ul>	<p>Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid, 10–25 mg by mouth once daily.</p> <p><u>Second-Line Alternative:</u></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin, 10–20 mg/kg body weight given twice daily by mouth 3 times per week</li> </ul>	<p>Consider discontinuing secondary prophylaxis in a patient receiving cART after sustained improvement from severe immunosuppression (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for longer than 6 months.</p> <p>In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no similar data exist for children. Thus, the recommended dosing for secondary prophylaxis in children is 1 mg/kg per dose (maximum 25 mg) once daily.</p> <p>Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.</p>
<b>Treatment</b>	TMP-SMX 5 mg/kg body weight of TMP component given twice daily by mouth for 10 days	<p>Pyrimethamine 1 mg/kg body weight plus folinic acid 10-25 mg by mouth once daily for 14 days</p> <p><u>Second-Line Alternatives:</u></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin 10–20 mg/kg body weight/day twice daily by mouth for 7 days</li> <li>• Nitazoxanide (see doses below) for 3 consecutive days               <ul style="list-style-type: none"> <li>• Children 1–3 years: 100 mg by mouth every 12 hours</li> <li>• Children 4–11 years: 200 mg by mouth every 12 hours</li> <li>• Adolescents ≥12 years and adults: 500 mg by mouth every 12 hours</li> </ul> </li> </ul>	<p>If symptoms worsen or persist, the TMP-SMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established.</p> <p>Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.</p>

**Key to Acronyms:** CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; cART = combination antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole