Cryptosporidiosis

Updated: August 29, 2019
Reviewed: August 29, 2019

Panel's Recommendations
I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent episodes of cryptosporidiosis? • Cryptosporidiosis can be prevented by practicing good hygiene (e.g., frequent handwashing), avoiding drinking water that might be contaminated, avoiding high-risk swimming exposures (e.g., drinking swimming water, especially in pools and water playgrounds frequented by very young children), and not eating food that might be contaminated (expert opinion). • Children with HIV infection should avoid contact with pre-weaned bovine calves, lambs, goat kids, ill animals, young dogs and cats, stray animals, and animal or human feces or any feces-contaminated surfaces (expert opinion). • In children with HIV infection, combination antiretroviral therapy (ART) to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric cryptosporidiosis (strong, low). II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat cryptosporidiosis? • Effective ART is the primary initial treatment for cryptosporidiosis in children (strong, moderate). • Nitazoxanide, in addition to ART, can be considered to treat cryptosporidiosis in children with HIV infection (strong, moderate). • Dehydration and electrolyte abnormalities should be corrected, and nutritional support should be provided as appropriate (expert opinion).
Rating System *Strength of Recommendation: Strong; Weak* *Quality of Evidence: High; Moderate; Low; or Very Low*

Epidemiology

Cryptosporidium spp. are protozoan parasites that primarily cause enteric illness (i.e., diarrhea) in humans and animals. *Cryptosporidium* spp. are distributed worldwide, and some species lack strict host specificity. The two species that infect humans most frequently are *Cryptosporidium hominis* and *Cryptosporidium parvum*. In addition, infections caused by *Cryptosporidium meleagridis*, *Cryptosporidium felis*, and *Cryptosporidium canis* have been reported in people with HIV infection. Among adults with HIV infection, risk of morbidity associated with *Cryptosporidium* infection is greatest in those with advanced immunosuppression, typically CD4 T lymphocyte (CD4) cell counts <100/mm^3.[1-3] *Cryptosporidium* primarily infects the distal small intestine and colon, but in immunocompromised hosts, extraintestinal involvement has been documented.

Infection occurs after ingestion of infectious oocysts that were excreted in the feces of infected animals and humans. The parasite is highly infectious, with an ID_{50} (median dose that will infect 50% of those exposed to the parasite) ranging from 9 to 1,042 oocysts for *C. parvum*,[4] and 10 to 83 oocysts for *C. hominis*.[5] Infection occurs when the ingested oocysts release sporozoites, which attach to and invade the intestinal epithelial cells. The parasite preferentially infects the ileum and colon.

Contact with infected persons (particularly children in diapers or in child care settings) or infected animals (particularly pre-weaned calves) is an important cryptosporidiosis risk factor.[6-11] *Cryptosporidium* oocysts can contaminate recreational water sources (such as swimming pools, water parks, and lakes) and drinking water supplies and cause infection when contaminated water is ingested. Oocysts are environmentally hardy and extremely chlorine tolerant. They can persist for days in swimming pools despite standard chlorination, and typical pool filtration systems do not efficiently remove oocysts. Multi-step treatment processes can be used to remove (i.e., flocculation and filtration) and inactivate (e.g., ultraviolet treatment) oocysts to protect public drinking water supplies and recreational water. Foodborne transmission, particularly involving unpasteurized apple cider, raw milk, and ill food handlers, has been documented. International travelers who drink the water in countries with less stringent drinking water treatment standards than the United States may might be at risk for *Cryptosporidium* infection.

In a serosurvey of multiple U.S. cities, 21.3% of children aged <10 years and 21.5% of those aged 11 to 20 years had detectable response to *Cryptosporidium* antigen.[12] Among immunocompetent pediatric patients with diarrhea in Oklahoma, 38% of those aged 5 to 13 years and 58% of those aged 14 to 21 years were seropositive for *Cryptosporidium* antibodies, compared with >80% of children aged 6 months to 13 years who resided near the U.S.–Mexican border and were seeking well-child care.[13,14] The incidence of reported cryptosporidiosis in the United States has dramatically increased since 2004, peaking at 4 cases per 100,000 people in 2007.[15] National cryptosporidiosis data from 1995 to 2012 demonstrated that there was a clear increase in cases reported during the period from 2005 to 2008, which persisted during the period from 2009 to 2012. Across all time periods, the highest rates were in children from birth to age 14 years, and cases were most frequently reported in children aged 1 to 4 years.[16] However, compared with earlier years, the rates in children decreased from 2009 through 2012.[17]

Transmission of *Cryptosporidium* occurs throughout the United States, with increased reporting in Midwestern states.[15,16] However, cryptosporidiosis is a highly underdiagnosed and underreported diarrheal illness. Infected patients can be asymptomatic, those with symptoms might not seek health care, health care providers might not request laboratory diagnostics when evaluating non-bloody diarrhea, requested ova and parasite testing might not include *Cryptosporidium* testing, and positive laboratory results are not always reported to public health officials.[16]

Before effective antiretroviral therapy (ART) became available, most patients with HIV diagnosed with cryptosporidiosis had advanced disease or AIDS. The incidence of cryptosporidiosis in people with HIV has declined dramatically since the introduction of ART.[18-20] During the pre-ART era, the rate of cryptosporidiosis was 0.6 cases per 100 patient-years in children followed in 13 Pediatric AIDS Clinical Trial Group (PACTG) trials (median age of 5.9 years and median CD4 count of 51/mm^3).[21] Data from the Perinatal AIDS Collaborative Transmission Study indicate that the rate of chronic intestinal cryptosporidiosis decreased from 0.2 cases per 100 person-years in the pre-ART era to 0.0 cases per 100 person-years in the post-ART era.[22] PACTG data estimated that the mortality rate in children with HIV infection significantly decreased from 7.2 to 0.8 per 100 person-years between 1994 and 2000 and subsequently stabilized through 2006.[23] The proportion of deaths due to all opportunistic infections decreased between 1994 and 2006, with declines most notable in deaths associated with *Cryptosporidium* and *Mycobacterium avium* complex (MAC). A recent prospective, comparative cross-sectional study of ART-treated versus ART-naive pediatric patients with HIV infection in Ethiopia found that *Cryptosporidium* infections were found only in ART-naive patients with low CD4 counts.[24]

Clinical Manifestations

Symptoms of cryptosporidiosis develop after an incubation period of approximately 1 week (range, 2 to 14 days). Diarrhea—which can be profuse, usually non-bloody, and watery—and weight loss, abdominal pain, anorexia, fatigue, joint pain, headache, fever, and vomiting have been reported in immunocompetent children and adults with *Cryptosporidium* infection.[25] In immunocompetent hosts, illness is self-limiting, and symptoms most often completely resolve within 2 to 3 weeks. Recurrence of symptoms after apparent resolution often has been reported. *Cryptosporidium* infection in children can have a significant impact on nutritional status and growth. A comparison of growth parameters in children with and without *C. parvum* infection in Peru showed that *C. parvum* infection has a lasting adverse effect on linear (height) growth, especially when acquired during infancy.[26] In a cohort of 405 schoolchildren aged 6 to 13 years in Mexico, children with cryptosporidiosis were 2.7 times more likely to be at risk of undernutrition by weight-for-age *z* score and 2.9 times more likely to be at risk of undernutrition by height-for-age *z* score than children without *Cryptosporidium* infection.[27]

Clinical presentation of cryptosporidiosis in patients with HIV infection varies with level of immunosuppression, ranging from no symptoms or transient disease to relapsing, chronic diarrhea or cholera- like diarrhea, which can lead to life-threatening wasting and malabsorption.[28] In immunocompromised children, chronic severe diarrhea can result in malnutrition, failure to thrive, and substantial intestinal fluid losses, resulting in severe dehydration and even death.

Different *Cryptosporidium* spp. and genotypes have been associated with different clinical manifestations. *C. hominis* was associated with vomiting in children without HIV in one study and in children and adults with HIV in a different study, whereas *C. parvum* infection was associated with vomiting in another study in adults with HIV.[29-31] Neither clinical history nor physical examination allows differentiation of cryptosporidial disease from that caused by other pathogens.

Biliary tract disease due to cryptosporidial infection is associated with CD4 counts ≤50/mm^3.[32] Symptoms and signs include fever, right upper abdominal pain, nausea, vomiting, and elevated alkaline phosphatase. Diagnostic studies show dilatation of the common bile duct, thickening of the gall bladder wall, and pericholecystic fluid collection. Pancreatitis is rare. Although cryptosporidial infection usually is limited to the gastrointestinal (GI) tract, respiratory disease has been reported in which no pathogen other than *Cryptosporidium* was detected in sputum.[33,34]

Diagnosis

Health care providers should specifically request *Cryptosporidium* testing because standard ova and parasite testing may not include *Cryptosporidium* spp. Though not extensively evaluated in children with HIV, diagnostic tests for *Cryptosporidium* are expected to perform similarly as in children without HIV.

Monoclonal antibody-based direct fluorescent assays and antigen-detection assays (such as enzyme-linked immunosorbent assay [EIA]) can be used to diagnose cryptosporidiosis because of their enhanced sensitivity and specificity as compared with microscopy.[35-38] Oocyst excretion can be intermittent; therefore, the parasite might not be detected in every stool, and stool specimens collected on 3 consecutive days should be examined before considering test results to be negative.[39] Some immunochromatography assays have been shown to have poor sensitivity and specificity.[40] With rapid test methods, confirmation by microscopy should be considered.

Commercially available multiplex molecular test panels for GI pathogens that include *Cryptosporidium* are now available. When compared with microscopy, the sensitivity for detection of parasitic pathogens was 91.7% for *Cryptosporidium*.[41] In a multicenter evaluation at four geographically distinct clinical sites across the United States, the panel demonstrated a sensitivity of 97.1% and specificity of 98.4% when compared with conventional PCR.[42] This methodology is becoming the new standard of care as it becomes more widely available.

Molecular characterization tools are being increasingly used to differentiate *Cryptosporidium* species in outbreak investigations and infection/contamination source tracking. *Cryptosporidium* isolates cannot be reliably genotyped or subtyped if stool is preserved in formalin, sodium acetate-acetic acid-formalin (SAF), or low-viscosity polyvinyl alcohol (LV-PVA).

Prevention Recommendations

Preventing Exposure

Caregivers and children with HIV infection should be educated and counseled about the different ways *Cryptosporidium* can be transmitted. Modes of transmission include having direct contact with fecal material from individuals with *Cryptosporidium* infection (particularly children's diapers) and from infected young animals, swallowing or drinking contaminated water, including during recreational activities, and eating contaminated food. Maternal infection with *Cryptosporidium* has been associated with infection in young infants demonstrating the importance of caregiver hygiene.[43]

Hand washing is probably the most important step to reduce the risk of *Cryptosporidium* infection. Children with HIV infection should always wash their hands before preparing or eating food; after using the toilet; after contact with children in diapers; after contact with clothing, bedding, toilets, or diapers soiled by anyone who has diarrhea; after touching pets or other animals; and after touching anything that might have come in contact with even the smallest amounts of human or animal feces (such as sand in a sandbox).

Children with HIV infection should avoid contact with pre-weaned bovine calves, other young animals (particularly dogs and cats aged <6 months and lambs and goat kids), ill animals, stray animals, and stool from any animals or humans or surfaces known to be contaminated with animal or human feces.[11] Children with HIV infection should avoid petting zoos and animal areas at farms and camps. However, if a child with HIV does visit an animal habitat, an immunocompetent caregiver should clean the child's shoes and any other surfaces possibly contaminated by feces (such as clothes and stroller wheels).

Children with HIV infection should avoid drinking water directly from ponds, streams, springs, lakes, or rivers, or swallowing water they swim or play in regardless of whether it is chlorinated. Caregivers and children with HIV infection should be aware that recreational water—including lakes, rivers, salt-water beaches, swimming pools, waterparks, hot tubs, spas, water playgrounds, and ornamental water fountains might be contaminated with human or animal feces that contain *Cryptosporidium*.

Some outbreaks of cryptosporidiosis have been linked to ingestion of water from contaminated municipal water supplies; the incidence of these outbreaks has dramatically decreased since the mid-1990s because of improved water treatment targeting the inactivation and removal of *Cryptosporidium*. To decrease the risk of cryptosporidiosis during outbreaks or when otherwise

advised by local public health officials to boil water, heat water used for preparing infant formula, drinking, making ice, etc. at a rolling boil for 1 minute. After the boiled water cools, put it in a clean bottle or pitcher with a lid and store it in the refrigerator. Water bottles and ice trays should be cleaned with soap and water before each use. Do not touch the inside of these containers after cleaning. Information on filtering tap water and home water distillers can be found on the Centers for Disease Control and Prevention (CDC) website at Prevention & Control: Immunocompromised Persons.

Nationally distributed brands of bottled or canned carbonated soft drinks are generally safe to drink. Commercially packaged, non-carbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those that can be stored unrefrigerated on grocery shelves) also are generally safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe water source. Fruit juices that must be refrigerated from the time they are processed to the time of consumption are either fresh (i.e., unpasteurized) or heat-treated (i.e., pasteurized); only juices labeled as pasteurized should be considered free of risk from *Cryptosporidium*. Other pasteurized beverages, such as milk, also are considered safe to drink.

All vegetables or fruit to be eaten uncooked should be thoroughly washed. If extra steps are required to make water safe, this safe water should be used to wash fruits and vegetables. When possible, fruit to be eaten raw should be peeled after washing. Unpasteurized dairy products, including raw milk, should not be consumed. Because cooking food kills *Cryptosporidium*, cooked food and heat-processed foods are generally safe if, after cooking or processing, they are not handled by someone infected with the parasite or exposed to contaminated water.

When traveling internationally, particularly in low-resource settings, people with HIV infection should be warned to avoid drinking tap water and also to not to use it to brush teeth. Ingesting ice made from tap water, raw fruits, and raw vegetables should also be avoided. Steaming-hot foods, self-peeled fruits, bottled and canned processed drinks, and hot coffee or hot tea are generally safe.

In hospitals, standard precautions are recommended. However, if the patient is diapered or incontinent, contact precautions should be used for the duration of illness. In addition, contact precautions may be used to control institutional outbreaks of cryptosporidiosis. Some experts recommend that severely immunocompromised patients with HIV not share a room with a patient with cryptosporidiosis because of the potential for fomite transmission. The potential for respiratory transmission of *Cryptosporidium* has been suggested.[34] However, no specific modifications to current prevention recommendations have been suggested.

Adolescents with HIV infection who are sexually active should be counseled about avoiding sexual practices that could result in oral exposure to feces (such as oral-anal contact). To reduce the risk of exposure to feces, adolescents should use dental dams or similar barrier methods for oral-anal and oral-genital contact, wear latex gloves during digital-anal contact, and change condoms after anal intercourse. Frequent washing of hands and genitals with warm, soapy water during and after sexual activities that could bring these body parts in contact with feces might further reduce the risk of *Cryptosporidium* infection.

Additional information on prevention can be found on CDC's website at Prevention & Control: Immunocompromised Persons.

Preventing Disease

Because chronic *Cryptosporidium* infection occurs most often in patients with HIV with advanced immunodeficiency, ART to prevent or reverse severe immune deficiency is a primary modality for prevention of *Cryptosporidium*-associated disease in children with HIV infection.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Immune reconstitution resulting from ART often results in clearance of *Cryptosporidium* infection. Effective ART is the primary initial treatment for these infections in children and adults with HIV infection who are not already receiving ART.[19,24,44] *In vitro* and observational studies, some of which are case series, suggest that ART containing a protease inhibitor (PI) might be preferable to other ART regimens because of a direct effect of the PI on the parasite.[44-53] PIs also increase production of interferon-gamma, which in turn inhibits *Cryptosporidium* infection. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Antimotility agents to combat malabsorption of nutrients and drugs should be used with caution.

Other than ART, there is no consistently effective therapy to treat cryptosporidiosis in patients with HIV infection.[54,55] Multiple agents have been investigated in small randomized controlled clinical trials in adults with HIV, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract.[56] Azithromycin and roxithromycin have also been investigated in small open- label studies.[57] No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has yet been shown consistently effective and durable when used alone without concomitant ART.[54,55] The duration of treatment in patients with HIV is also uncertain.

While no agent has consistent, proven efficacy for treating cryptosporidiosis in immunocompromised patients, including patients with HIV, nitazoxanide has been shown to reduce the load of parasites and was associated with clinical improvement in some studies in populations with and without HIV infection.[58] An Egyptian clinical trial in 100 adults and children without HIV infection randomized patients to a 3-day course of nitazoxanide or placebo.[59] Nitazoxanide therapy reduced the duration of both diarrhea and oocyst shedding; in children, clinical response was 88% with nitazoxanide and 38% with placebo. No severe adverse events were reported, and adverse events that were reported were similar in the treatment and placebo groups in this study. A study in Zambia in 100 malnourished children (half of whom had HIV) aged 12 to 35 months reported a clinical response in 56% of children without HIV treated with nitazoxanide and in 23% of those receiving placebo.[60] However, in the children with HIV infection, no benefit from nitazoxanide was observed (clinical response in 8% treated with nitazoxanide and in 25% receiving placebo). In a subsequent study of 60 children with HIV with cryptosporidiosis, the same investigators reported no significant benefit using twice the recommended dose administered for 28 days.[61] It should be noted that the children in the Zambian studies were not receiving ART. In a study in adults with HIV not receiving ART who had CD4 counts >50 cells/mm^3, the administration of 14 days of nitazoxanide resulted in a parasitological cure rate of 71% (10 of 14 patients) at a dose of 500 mg twice daily and 90% (9 of 10 patients) at a

dose of 1,000 mg twice daily as compared with 20% among placebo recipients.[62] In a cohort of 365 HIV-positive patients aged >3 years with *Cryptosporidium* infection who received nitazoxanide as part of a compassionate use program in the United States, sustained clinical response while on treatment was achieved in 59% of the patients. Clinical response was associated with negative stools ($P < 0.0001$). In this cohort, nitazoxanide was found to be safe at higher doses (up to 3,000 mg/day) and for long durations of treatment.[63]

Given the seriousness of this infection in immunocompromised individuals and the potential benefit suggested in some studies, use of nitazoxanide should be considered in immunocompromised children with HIV infection (in conjunction with ART for immune restoration).[54,55] Given that ART might directly inhibit the parasite, it is possible that the combination of ART and parasitic therapy might be synergistic. Nitazoxanide is approved in the United States to treat diarrhea caused by *Cryptosporidium* and *Giardia lamblia* in immunocompetent children aged ≥1 year and is available in liquid and tablet formulations. The recommended dose for children is 100 mg twice daily for children aged 1 to 3 years and 200 mg twice daily for children aged 4 to 11 years. A tablet preparation (500 mg twice daily) is available for children aged ≥12 years. Nitazoxanide should be administered with food.

Paromomycin, a non-absorbable aminoglycoside indicated for the treatment of intestinal amoebiasis, is not approved for treatment of cryptosporidiosis. Two small, randomized trials evaluating the efficacy of paromomycin for treatment of patients with HIV infection found clinical improvement or reduced oocyst excretion in those treated with paromomycin.[64,65] However, other reports of paromomycin treatment in patients with HIV infection found repeated failure to cure.[66] Therefore, data do not support a recommendation for use of paromomycin for cryptosporidiosis. Clinical or parasitological cure has been documented with use of paromomycin and azithromycin in combination in case series of patients with HIV with cryptosporidial diarrhea and case reports of patients with HIV with pulmonary cryptosporidiosis.[67-69]

Monitoring and Adverse Events, Including IRIS

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte imbalance, malnutrition, and weight loss. In severely ill patients, total parenteral nutrition might be indicated. One case report describes immune reconstitution inflammatory syndrome, specifically terminal ileitis, in association with treatment of cryptosporidiosis.[70]

In general, nitazoxanide is well tolerated and side effects are mild, transient, and generally limited to the GI tract.

Managing Treatment Failure

The most important steps for managing treatment failure are optimizing ART to increase CD4 counts and providing supportive treatment.

Preventing Recurrence

No pharmacologic interventions, other than ART to prevent or reverse severe immune deficiency, are known to be effective in preventing recurrence of cryptosporidiosis. Good hygiene, including frequent handwashing, and avoiding potentially contaminated water and food and high-risk environmental contact can help prevent reinfection.

Discontinuing Secondary Prophylaxis

Not applicable.

Recommendations

I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent episodes of cryptosporidiosis?

- Cryptosporidiosis can be prevented by practicing good hygiene (e.g., frequent handwashing), avoiding drinking water that might be contaminated, avoiding high risk swimming exposures (e.g., drinking swimming water, especially in pools and water playgrounds frequented by very young children), and not eating food that might be contaminated **(expert opinion).**
- Children with HIV infection should avoid contact with pre-weaned bovine calves, lambs, goat kids, ill animals, young dogs and cats, stray animals, and stool from any animals or humans or surfaces known to be contaminated with human or animal feces **(expert opinion).**
- ART for children with HIV infection to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric cryptosporidiosis **(strong, low).**

  A prospective, comparative cross-sectional study of ART-treated versus ART-naive pediatric patients with HIV infection in Ethiopia found that *Cryptosporidium* infections were found only in ART-naive patients with low CD4 counts.[24] A retrospective/prospective cohort study in adults with HIV infection in South Ethiopia demonstrated that patients who initiated ART with a CD4 count of <500/mm^3 and received health interventions including provision of household water treatment, safe water storage, soap, and anti- helminthic drugs had decreased rate of cryptosporidiosis, even among patients with CD4 counts <200 cells/mm^3.[71]

II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat cryptosporidiosis?

- Treatment with ART is the best intervention in children with HIV infection and cryptosporidiosis **(strong, moderate).**
- Immune reconstitution resulting from ART often results in clearance of Cryptosporidium infection, and ART is the primary initial treatment for these infections in children with HIV infection who are not already receiving ART.[19,24,44]
- Nitazoxanide, in addition to ART, can be considered for cryptosporidiosis in children with HIV **(strong, moderate).**

  A clinical trial comparing nitazoxanide versus placebo in children without HIV infection demonstrated that resolution of diarrhea and parasitologic cure were significantly higher in children treated with nitazoxanide.[59] In a prospective cohort of patients with HIV infection with cryptosporidiosis treated with nitazoxanide, sustained clinical response was achieved in 59% of patients, and 57% of patients had *Cryptosporidium*-negative stool before completing the study.[63] However, a study of malnourished Zambian children demonstrated no benefit from nitazoxanide among children with HIV (clinical response in 8% treated with nitazoxanide and in 25% receiving placebo) but did show benefit when both children with and without HIV infection were included.[60]

- Dehydration and electrolyte abnormalities should be corrected, and nutritional support should be provided as appropriate **(expert opinion).**

  There are no studies that address this specific management issue in cryptosporidiosis. However, recognition and management of hydration status, electrolyte imbalance, and nutritional needs are key to management of infectious diarrhea.

References

1. Flanigan T, Whalen C, Turner J, et al. *Cryptosporidium* infection and CD4 counts. *Ann Intern Med*. 1992;116(10):840- 842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1348918.

2. Sorvillo F, Beall G, Turner PA, et al. Seasonality and factors associated with cryptosporidiosis among individuals with HIV infection. *Epidemiol Infect*. 1998;121(1):197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9747773.

3. Inungu JN, Morse AA, Gordon C. Risk factors, seasonality, and trends of cryptosporidiosis among patients infected with human immunodeficiency virus. *Am J Trop Med Hyg*. 2000;62(3):384-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11037782.

4. Okhuysen PC, Chappell CL, Crabb JH, Sterling CR, DuPont HL. Virulence of three distinct *Cryptosporidium parvum* isolates for healthy adults. *J Infect Dis*. 1999;180(4):1275-1281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10479158.

5. Chappell CL, Okhuysen PC, Langer-Curry R, et al. *Cryptosporidium* hominis: experimental challenge of healthy adults. *Am J Trop Med Hyg*. 2006;75(5):851-857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17123976.

6. Heijbel H, Slaine K, Seigel B, et al. Outbreak of diarrhea in a day care center with spread to household members: the role of *Cryptosporidium*. *Pediatr Infect Dis J*. 1987;6(6):532-535. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3615068.

7. O'Connor R M, Shaffie R, Kang G, Ward HD. Cryptosporidiosis in patients with HIV/AIDS. *AIDS*. 2011;25(5):549-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21160413.

8. Roy SL, DeLong SM, Stenzel SA, et al. Risk factors for sporadic cryptosporidiosis among immunocompetent persons in the United States from 1999 to 2001. *J Clin Microbiol*. 2004;42(7):2944-2951. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15243043.

9. Wang L, Zhang H, Zhao X, et al. Zoonotic *Cryptosporidium* species and Enterocytozoon bieneusi genotypes in HIV- positive patients on antiretroviral therapy. *J Clin Microbiol*. 2013;51(2):557-563. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23224097.

10. Wanyiri JW, Kanyi H, Maina S, et al. Cryptosporidiosis in HIV/AIDS patients in Kenya: clinical features, epidemiology, molecular characterization and antibody responses. *Am J Trop Med Hyg*. 2014;91(2):319-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24865675.

11. Jacob J, Lorber B. Diseases transmitted by man's best friend: the dog. *Microbiol Spectr*. 2015;3(4). Available at: https:// www.ncbi.nlm.nih.gov/pubmed/26350317.

12. Frost FJ, Muller TB, Calderon RL, Craun GF. Analysis of serological responses to *Cryptosporidium* antigen among NHANES III participants. *Ann Epidemiol*. 2004;14(7):473-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15310525.

13. Kuhls TL, Mosier DA, Crawford DL, Griffis J. Seroprevalence of cryptosporidial antibodies during infancy, childhood, and adolescence. *Clin Infect Dis*. 1994;18(5):731-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8075261.

14. Leach CT, Koo FC, Kuhls TL, Hilsenbeck SG, Jenson HB. Prevalence of *Cryptosporidium parvum* infection in children along the Texas-Mexico border and associated risk factors. *Am J Trop Med Hyg*. 2000;62(5):656-661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11289680.

15. Painter JE, Hlavsa MC, Collier SA, et al. Cryptosporidiosis surveillance -- United States, 2011-2012. *MMWR Suppl*. 2015;64(3):1-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25928581.

16. Yoder JS, Beach MJ. *Cryptosporidium* surveillance and risk factors in the United States. *Exp Parasitol*. 2010;124(1):31-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786022.

17. Painter JE, Gargano JW, Yoder JS, Collier SA, Hlavsa MC. Evolving epidemiology of reported cryptosporidiosis cases in the United States, 1995-2012. *Epidemiol Infect*. 2016;144(8):1792-1802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27125575.

18. Huang DB, White AC. An updated review on *Cryptosporidium* and Giardia. *Gastroenterol Clin North Am*. 2006;35(2):291-314, viii. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16880067.

19. Chen XM, Keithly JS, Paya CV, LaRusso NF. Cryptosporidiosis. *N Engl J Med*. 2002;346(22):1723-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12037153.

20. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. 2010;24(10):1549-1559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20502317.

21. Dankner WM, Lindsey JC, Levin MJ, Pediatric ACTGPT. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2001;20(1):40-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11176565.

22. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986- 2004. *Pediatrics*. 2007;120(1):100-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17606567.

23. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr*. 2010;53(1):86-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20035164.

24. Mengist HM, Taye B, Tsegaye A. Intestinal parasitosis in relation to CD4+T cells levels and anemia among HAART initiated and HAART naive pediatric HIV patients in a Model ART center in Addis Ababa, Ethiopia. *PLoS One*. 2015;10(2):e0117715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25658626.

25. Hunter PR, Hughes S, Woodhouse S, et al. Health sequelae of human cryptosporidiosis in immunocompetent patients. *Clin Infect Dis*. 2004;39(4):504-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15356813.

26. Checkley W, Epstein LD, Gilman RH, Black RE, Cabrera L, Sterling CR. Effects of *Cryptosporidium parvum* infection in Peruvian children: growth faltering and subsequent catch-up growth. *Am J Epidemiol*. 1998;148(5):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9737562.

27. Quihui-Cota L, Lugo-Flores CM, Ponce-Martinez JA, Morales-Figueroa GG. Cryptosporidiosis: a neglected infection and its association with nutritional status in schoolchildren in northwestern Mexico. *J Infect Dev Ctries*. 2015;9(8):878- 883. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26322881.

28. Hunter PR, Nichols G. Epidemiology and clinical features of *Cryptosporidium* infection in immunocompromised patients. *Clin Microbiol Rev*. 2002;15(1):145-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11781272.

29. Cama VA, Ross JM, Crawford S, et al. Differences in clinical manifestations among *Cryptosporidium* species and subtypes in HIV-infected persons. *J Infect Dis*. 2007;196(5):684-691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17674309.

30. Cama VA, Bern C, Roberts J, et al. *Cryptosporidium* species and subtypes and clinical manifestations in children, Peru. *Emerg Infect Dis*. 2008;14(10):1567-1574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18826821.

31. Adamu H, Petros B, Zhang G, et al. Distribution and clinical manifestations of *Cryptosporidium* species and subtypes in HIV/AIDS patients in Ethiopia. *PLoS Negl Trop Dis*. 2014;8(4):e2831. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24743521.

32. Vakil NB, Schwartz SM, Buggy BP, et al. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. *N Engl J Med*. 1996;334(1):19-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7494565.

33. Clavel A, Arnal AC, Sanchez EC, et al. Respiratory cryptosporidiosis: case series and review of the literature. *Infection*. 1996;24(5):341-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8923043.

34. Mor SM, Tumwine JK, Ndeezi G, et al. Respiratory cryptosporidiosis in HIV-seronegative children in Uganda: potential for respiratory transmission. *Clin Infect Dis*. 2010;50(10):1366-1372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20377408.

35. Weber R, Bryan RT, Bishop HS, Wahlquist SP, Sullivan JJ, Juranek DD. Threshold of detection of *Cryptosporidium* oocysts in human stool specimens: evidence for low

sensitivity of current diagnostic methods. *J Clin Microbiol*. 1991;29(7):1323-1327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1715881.

36. Arrowood MJ, Sterling CR. Comparison of conventional staining methods and monoclonal antibody-based methods for *Cryptosporidium* oocyst detection. *J Clin Microbiol*. 1989;27(7):1490-1495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2475523.

37. Garcia LS, Shimizu RY. Evaluation of nine immunoassay kits (enzyme immunoassay and direct fluorescence) for detection of Giardia lamblia and Cryptosporidium parvum in human fecal specimens. J Clin Microbiol. 1997;35(6):1526-1529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9163474.

38. Garcia LS, Shimizu RY, Novak S, Carroll M, Chan F. Commercial assay for detection of Giardia lamblia and *Cryptosporidium parvum* antigens in human fecal specimens by rapid solid-phase qualitative immunochromatography. *J Clin Microbiol*. 2003;41(1):209-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12517850.

39. van Gool T, Weijts R, Lommerse E, Mank TG. Triple Faeces Test: an effective tool for detection of intestinal parasites in routine clinical practice. *Eur J Clin Microbiol Infect Dis*. 2003;22(5):284-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12736794.

40. Robinson TJ, Cebelinski EA, Taylor C, Smith KE. Evaluation of the positive predictive value of rapid assays used by clinical laboratories in Minnesota for the diagnosis of cryptosporidiosis. *Clin Infect Dis*. 2010;50(8):e53-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20218890.

41. Claas EC, Burnham CA, Mazzulli T, Templeton K, Topin F. Performance of the xTAG(R) gastrointestinal pathogen panel, a multiplex molecular assay for simultaneous detection of bacterial, viral, and parasitic causes of infectious gastroenteritis. *J Microbiol Biotechnol*. 2013;23(7):1041-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23711521.

42. Buss SN, Leber A, Chapin K, et al. Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. *J Clin Microbiol*. 2015;53(3):915-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25588652.

43. Pedersen SH, Wilkinson AL, Andreasen A, et al. *Cryptosporidium* prevalence and risk factors among mothers and infants 0 to 6 months in rural and semi-rural Northwest Tanzania: a prospective cohort study. *PLoS Negl Trop Dis*. 2014;8(10):e3072. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25275519.

44. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;25(2):124-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11103042.

45. Hommer V, Eichholz J, Petry F. Effect of antiretroviral protease inhibitors alone, and in combination with paromomycin, on the excystation, invasion and *in vitro* development of

Cryptosporidium parvum. *J Antimicrob Chemother*. 2003;52(3):359-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12888587.

46. Mele R, Gomez Morales MA, Tosini F, Pozio E. Indinavir reduces *Cryptosporidium parvum* infection in both *in vitro* and *in vivo* models. *Int J Parasitol*. 2003;33(7):757-764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12814654.

47. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. 2000;19(3):213-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10795595.

48. Cabada MM, White AC, Jr. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis*. 2010;23(5):494-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20689422.

49. Maggi P, Larocca AM, Ladisa N, et al. Opportunistic parasitic infections of the intestinal tract in the era of highly active antiretroviral therapy: is the CD4(+) count so important? *Clin Infect Dis*. 2001;33(9):1609-1611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11588705.

50. Miao YM, Awad-El-Kariem FM, Gibbons CL, Gazzard BG. Cryptosporidiosis: eradication or suppression with combination antiretroviral therapy? *AIDS*. 1999;13(6):734-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10397573.

51. Bobin S, Bouhour D, Durupt S, Boibieux A, Girault V, Peyramond D. [Importance of antiproteases in the treatment of microsporidia and/or cryptosporidia infections in HIV-seropositive patients]. *Pathol Biol (Paris)*. 1998;46(6):418-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9769873.

52. Foudraine NA, Weverling GJ, van Gool T, et al. Improvement of chronic diarrhoea in patients with advanced HIV-1 infection during potent antiretroviral therapy. *AIDS*. 1998;12(1):35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9456253.

53. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet*. 1998;351(9098):256-261. Available at: http://www. ncbi.nlm.nih.gov/pubmed/9457096.

54. Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane Database Syst Rev. 2007(1):CD004932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17253532.

55. Abubakar I, Aliyu SH, Arumugam C, Usman NK, Hunter PR. Treatment of cryptosporidiosis in immunocompromised individuals: systematic review and meta-analysis. Br J Clin Pharmacol. 2007;63(4):387-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17335543.

56. Pantenburg B, Cabada MM, White AC, Jr. Treatment of cryptosporidiosis. *Expert Rev Anti Infect Ther*. 2009;7(4):385-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19400754.

57. Rossignol JF. *Cryptosporidium* and Giardia: treatment options and prospects for new drugs. *Exp Parasitol*. 2010;124(1):45-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632225.

58. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis*. 2005;40(8):1173-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15791519.

59. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. 2001;184(1):103-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11398117.

60. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*. 2002;360(9343):1375-1380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12423984.

61. Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis*. 2009;9:195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19954529.

62. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. *Trans R Soc Trop Med Hyg*. 1998;92(6):663-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10326116.

63. Rossignol JF. Nitazoxanide in the treatment of acquired immune deficiency syndrome-related cryptosporidiosis: results of the United States compassionate use program in 365 patients. *Aliment Pharmacol Ther*. 2006;24(5):887-894. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16918894.

64. White AC, Jr., Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. *J Infect Dis*. 1994;170(2):419-424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8035029.

65. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trial Group. *Clin Infect Dis*. 2000;31(4):1084-1092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11049793.

66. Hashmey R, Smith NH, Cron S, Graviss EA, Chappell CL, White AC, Jr. Cryptosporidiosis in Houston, Texas. A report of 95 cases. *Medicine (Baltimore)*. 1997;76(2):118-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9100739.

67. Smith NH, Cron S, Valdez LM, Chappell CL, White AC, Jr. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis*. 1998;178(3):900-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9728569.

68. Meamar AR, Rezaian M, Rezaie S, et al. *Cryptosporidium parvum* bovine genotype oocysts in the respiratory samples of an AIDS patient: efficacy of treatment with a combination of azithromycin and paromomycin. *Parasitol Res*. 2006;98(6):593-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16416289.

69. Palmieri F, Cicalini S, Froio N, et al. Pulmonary cryptosporidiosis in an AIDS patient: successful treatment with paromomycin plus azithromycin. *Int J STD AIDS*. 2005;16(7):515-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16004637.

70. Plasencia LD, Socas Mdel M, Valls RA, Fernandez EM, Higuera AC, Gutierrez AB. Terminal ileitis as a manifestation of immune reconstitution syndrome following HAART. *AIDS*. 2006;20(14):1903-1905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16954736.

71. Shimelis T, Tassachew Y, Lambiyo T. *Cryptosporidium* and other intestinal parasitic infections among HIV patients in southern Ethiopia: significance of improved HIV-related care. *Parasit Vectors*. 2016;9(1):270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27165271.

Dosing Recommendations for Prevention and Treatment of Cryptosporidiosis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	ARV therapy to avoid advanced immune deficiency	N/A	N/A
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	Effective ART • Immune reconstitution might lead to parasitologic and clinical response	There is no consistently effective therapy for cryptosporidiosis in patients with HIV infection; optimized ART and a trial of nitazoxanide should be considered. Nitazoxanide • 1–3 years of age: Nitazoxanide (20 mg/ mL oral solution) 100 mg orally twice daily with food • 4–11 years of age: Nitazoxanide (20 mg/ mL oral solution) 200 mg orally twice daily with food • ≥12 years of age: Nitazoxanide tablet 500 mg orally twice daily with food *Treatment Duration* • 3–14 days	Supportive Care • Hydration, correct electrolyte abnormalities, nutritional support Antimotility agents (such as loperamide) should be used with caution in young children.

Key: ARV = antiretroviral; ART = antiretroviral therapy