



Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. In 2006, the World Health Organization estimated that out of a global population of 6.6 billion, 1.2 billion individuals live in areas where malaria is highly endemic (defined as 1 or more cases per 1,000 people per year) and 2.1 billion individuals live in areas of some risk of malaria transmission.¹ Of the nearly 250 million cases of malaria worldwide in 2006 (based on reports and models), between 152 million and 287 million occurred in Africa, the area of the world with the highest HIV prevalence.¹ The global case-fatality rate was 4 deaths/10,000 infections per year, with ~90% of deaths occurring in Africa and 85% of those deaths in children younger than 5 years of age. Current attributable morbidity and mortality likely is an underestimate, given our limited understanding, surveillance, and reporting of non-falciparum infections.

Malaria typically is transmitted by the bite of an infected female *Anopheles sp.* mosquito. Reports of vertical transmission and infection after blood transfusion do exist, but these routes of transmission are uncommon in non-endemic areas.²⁻⁵

Malaria in humans can be caused by any one of the five species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* (a zoonotic species that also infects macaques in Southeast Asia).⁵ Although *P. vivax* infections are more common and occur in a far wider geographic distribution,⁶ *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections. *P. vivax*, however, should not be discounted as a risk for travelers in many parts of the world.

Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given this substantial overlap, even modest interactions between them have public health importance.^{7,8} Malaria influences the natural history of HIV infection, and HIV infection alters the natural history and severity of malaria.⁹

Many foreign-born individuals develop malaria in the United States because of distant exposure before their arrival, or as a result of more recent travel for business or family reasons. Similarly, U.S.-born individuals can develop malaria during travel to endemic areas.¹⁰⁻¹³ Failure to take appropriate chemoprophylaxis is a common problem for both groups of individuals.^{14,15} People who formerly lived in malarious areas may believe that they are immune, and therefore, do not need to take prophylaxis.¹⁶ Such patients are at high risk of infection, however, because they likely have lost partial immunity within 6 months after leaving endemic regions.

Consideration of malaria in returning travelers who are febrile is important: Of the nearly 50 million individuals who travel to developing countries each year, between 5% and 11% develop a fever during or after travel.¹⁷⁻²⁰ Malaria is a surprisingly common cause of these fevers.²¹

Clinical Manifestations

The clinical syndromes caused by *Plasmodium* species depend on prior exposure.²² While many native U.S. travelers have no prior immunity, clinical manifestations in those who have resided in malarious areas depend on whether they lived in an area with stable endemic malaria transmission (year round) or unstable (seasonal, infrequent or very low) transmission.²³

In stable endemic areas, children younger than age 5 years may experience chronic infections with recurrent parasitemia, resulting in severe anemia and death. Children who survive these infections usually acquire partial immunity by age 5 years, and if they remain in the area where malaria is endemic, maintain this immunity into adulthood. In stable endemic areas, adults usually experience asymptomatic or milder infections as a result of this acquired immune response. However, as noted previously, patients who leave

endemic areas and subsequently return may be at high risk of disease because they likely have lost partial immunity 6 months after leaving endemic regions.

In unstable transmission areas, protective immunity is not acquired. For populations in these areas, the overwhelming clinical manifestation is acute febrile disease that can be complicated by cerebral malaria, affecting persons of all ages.

When pregnant women in areas of unstable transmission develop acute malaria, the consequences may include spontaneous abortion and stillbirth. In more stable transmission areas, pregnant women, particularly primigravidas, may lose some acquired immunity. Although infections may continue to be asymptomatic, infected pregnant women may acquire placental malaria that contributes to intrauterine growth retardation, low birth weight, and increased infant mortality.

Patients with malaria can exhibit various symptoms and a broad spectrum of severity, depending upon factors such as the infecting species and level of acquired immunity in the host. HIV-immunosuppressed patients in endemic areas may lose acquired malarial immunity, and HIV-immunosuppressed adults with little or no previous malaria exposure (such as travelers) appear to be at increased risk of severe outcomes.²⁴

The incubation period for *P. falciparum* is from a week to several months, but most often less than 60 days. Patients can present much later (>1 year), but this pattern is more common with other species, especially *P. vivax*. In non-immune patients, typical symptoms of malaria include fever, chills, myalgias and arthralgias, headache, diarrhea, vomiting, and other non-specific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also may be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* malaria; those with *P. malariae* occur every 72 hours. This classic presentation is highly variable, however, and may not be present. *P. knowlesi*, known to cause human infection in Southeast Asia in travelers to jungle/forested areas, is clinically indistinguishable from other species of malaria, and the overwhelming majority of patients present with uncomplicated disease (~90%).²⁵

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with central nervous system symptoms can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in patients infected with *P. falciparum*; in Africa, case fatality rates with cerebral malaria approach 40%.²⁶⁻²⁸ The risk of severe and complicated illness is increased in patients with high levels of parasitemia and without partial immunity. Metabolic acidosis is an important manifestation of severe malaria and an indicator of poor prognosis.²⁹ Other acute complications include renal failure, hypoglycemia, disseminated intravascular coagulation, shock, and acute pulmonary edema.³⁰ *P. falciparum* is the species most commonly responsible for severe disease and death although the other species can cause severe disease and death too.^{25,31}

Effect of HIV on Parasitemia and Clinical Severity

HIV infection impairs acquired immunity to malaria that is present in older children and adults in stable endemic areas. Large cohort studies have demonstrated the increased frequency (with rates one- to two-fold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher-density parasitemia associated with more advanced immunosuppression, particularly among those with CD4 T-lymphocyte (CD4) cell counts <350 cells/mm³.³²⁻³⁴ Increased rates of malaria among individuals with HIV do not appear to be as great as observed with classic opportunistic infections such as tuberculosis and *Pneumocystis jirovecii* pneumonia.³⁵

In a prospective cohort study in an area with unstable malaria transmission, HIV-infected non-immune adults were found to be at increased risk of severe malaria, and the risk was associated with a low CD4 cell count.³⁶ Non-immune HIV-infected patients were substantially more likely to have severe clinical malaria than were non-immune patients without HIV. In KwaZulu Natal, an area of unstable malaria transmission, HIV-infected adults hospitalized for malaria were substantially more likely to die or require an intensive care unit admission than those who were not HIV-infected.³⁷ In contrast, HIV infection did not confer an increased

risk of poor outcomes among partially immune adults in areas with more stable transmission.³² In a cross-sectional study of travelers returning to France from malaria-endemic areas between 2000 and 2003, HIV-infected individuals with CD4 counts <350 cells/mm³ were at significantly higher risk of developing severe malaria, compared with those who were HIV-negative.³⁴

Effects of Malaria on Mother-to-Child HIV Transmission

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages³⁸ and increased viral load,³⁹ raising the possibility of placental malaria leading to increased mother-to-child transmission (MTCT) of HIV. However, data are conflicting concerning the effect of malaria during pregnancy on risk of MTCT. One study in Uganda demonstrated increased MTCT in women with placental malaria,⁴⁰ but studies from Kenya did not demonstrate this association.^{41,42}

Diagnosis

A malaria diagnosis must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from individuals who have been to such areas.

Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, polymerase chain reaction based assays, and serologic tests.

Direct microscopic examination of intracellular parasites on stained blood films is the standard for definitive diagnosis in nearly all settings because it allows for identification of the species and provides a measure of parasite density. Microscopic diagnosis of *P. knowlesi* is difficult because it is commonly misidentified as *P. malariae*, which tends to follow a more benign course. Providers should have a high index of suspicion for *P. knowlesi* in travelers returning from Southeast Asia.³¹

In non-immune patients with all types of malaria, symptoms may develop before detectable levels of parasitemia are evident. For this reason, several blood smear examinations taken at 12- to 24-hour intervals may be needed to positively rule out a diagnosis of malaria in symptomatic patients. Guidelines for laboratory diagnosis are summarized elsewhere and are available at Centers for Disease Control and Prevention (CDC)'s malaria website (<http://www.cdc.gov/malaria>). Rapid diagnostic tests, particularly for the diagnosis of *P. falciparum*, can be used depending on the local expertise and practice and can facilitate prompt diagnosis and treatment of infected patients, but must be followed by microscopy.

Preventing Exposure

Pre-travel evaluation by a travel medicine specialist can provide specific education about risk of exposure in various geographic locales, the utility of insecticide-impregnated bed nets in the setting where the individual will be traveling or residing, and the use of DEET (N,N-diethyl-3-methyl-benzamide)-containing repellants.

Infection with *P. falciparum* can be more severe in HIV-infected patients with low CD4 cell counts and in pregnant women regardless of HIV infection than in other individuals. Because no chemoprophylactic regimen is completely effective, HIV-infected patients with low CD4 cell counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible (**AIII**). If travel to an endemic area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

For United States travelers (including HIV-infected patients) to endemic areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. Recommendations for prophylaxis are the same for HIV-infected patients as for those who are not HIV-

infected and are available at CDC's malaria website (AIII) (<http://www.cdc.gov/malaria>).

Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.⁴³ A recent study of HIV-infected patients in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, and then reduced another 50% when antiretroviral (ARV) drugs were provided, and finally reduced another 50% with provision of insecticide-treated nets.⁴⁴ However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the recommended antimalarials. Therefore, HIV-infected travelers should not rely on prophylaxis with cotrimoxazole for chemoprophylaxis against malaria (AIII).

Treating Disease

Because *P. falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment (AIII). Diagnosis prior to treatment should always be pursued; however, treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed (AIII).

Choice of treatment is guided by the degree of parasitemia and the species of *Plasmodium* identified, a patient's clinical status, and the likely drug susceptibility of the infecting species (as determined by where the infection was acquired).

For HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients (AIII). CDC posts current treatment recommendations on its website (<http://www.cdc.gov/malaria>) and has clinicians on call 24 hours to provide advice to clinicians on diagnosing and treating malaria (CDC Malaria Hotline: (770) 488-7788; Monday through Friday, 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours).

Special Considerations with Regard to Starting Antiretroviral Therapy (ART)

There is no reason to defer ART initiation after patients have recovered from acute malaria.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Careful monitoring of patients (especially those with *P. falciparum* malaria) is necessary, including measurement of peripheral parasitemia and hemoglobin and blood glucose levels, as well as assessment of cerebral, pulmonary, and renal function. Frequency of monitoring depends on severity of disease, a patient's immune status, and the species of *Plasmodium*.

Chemoprophylaxis or treatment for malaria in patients receiving ARV agents requires attention to potential drug interactions (see [Table 5](#)). Several potential drug interactions can occur between antimalarial and HIV drugs.⁴⁵ Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at www.hiv-druginteractions.org. Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Insufficient data are available to suggest that dose adjustments are needed.

Quinine levels may be increased by ritonavir-containing regimens; conversely, nevirapine and efavirenz can reduce plasma quinine levels. Potential interactions can occur between ritonavir and chloroquine, but their clinical significance is unclear, and until further data are available, no dose adjustments are recommended.

Artemether-lumefantrine is now approved in the United States for treatment of uncomplicated *P. falciparum* infection. Data in children suggest that this combination is well tolerated and safe in HIV-infected children,⁴⁶ but data are lacking in HIV-infected adults. Artesunate is available for treatment of severe malaria through a compassionate use Investigational New Drug application. A trial in Uganda demonstrated the effectiveness of artesunate plus amodiaquine in HIV-infected children, but treatment was associated with increased risk of

neutropenia in those on ART, particularly zidovudine, which was attributed to the amodiaquine component of therapy.⁴⁷

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors have the potential to affect metabolism of artemisinin-containing drugs,⁴⁸ but the overall effect and clinical significance remain unclear. No dose alterations currently are recommended.

No immune reconstitution inflammatory syndrome (IRIS) has been described in association with malaria.

Managing Treatment Failure

HIV-infected individuals are at increased risk of malaria treatment failure.⁴⁹ Management of treatment failure is the same in HIV-infected and HIV-uninfected patients, except for considerations about drug interactions between ART and antimalarial drugs. Drug-resistant malaria and possible concomitant infections should be considered in HIV-infected patients whose malaria fails to respond to therapy.

Preventing Recurrence

If the species of malaria identified is *P. vivax* or *P. ovale*, which can cause recurrence due to hepatic phase of infection, then treatment with primaquine in addition to standard treatment is recommended to prevent recurrence (**AI**). Guidelines for primaquine treatment do not differ in HIV-infected individuals.

Special Considerations During Pregnancy

Malaria in pregnancy affects both mother and fetus. Infection with *P. falciparum* during pregnancy can increase maternal risk of severe disease and anemia and risk for stillbirth, preterm birth, and low birth weight.⁵⁰ The diagnosis of malaria in pregnant women is the same as in women who are not pregnant.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended.⁵¹ For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with quinine for 7 days is recommended. For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended.

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk of birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe.^{51,52} Because of the potential for hypoglycemia, glucose levels should be monitored in pregnant women treated with quinine and their neonates. Clindamycin use has not been associated with birth defects. Animal and human data on use of prophylactic and treatment doses of mefloquine do not suggest teratogenicity and the drug can be used safely during all trimesters.⁵³ Because of limited data, atovaquone-proguanil is not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin, quinine monotherapy or mefloquine are unavailable or not tolerated.⁵² Tetracyclines are not recommended in pregnancy because of increased risk of maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal glucose-6-phosphate dehydrogenase (G6PD) deficiency.

After treatment, all pregnant women with *P. vivax* and *P. ovale* should receive chloroquine prophylaxis for the duration of pregnancy to avoid relapses. Once-weekly mefloquine can be used for prophylaxis in pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains. Women who have normal G6PD screening tests can be treated with primaquine after delivery.

Recommendations for Preventing and Treating Malaria

Preventing Malaria in Patients Traveling to Endemic Areas:

- Recommendations are the same for HIV-infected and HIV-uninfected patients.
- Specific recommendations are based on region of travel, malaria risks, and drug susceptibility in the region.
- Clinicians should refer to the following website for the most up-to-date recommendations: <http://www.cdc.gov/malaria>
- TMP-SMX has been shown to reduce malaria in HIV infected adults in Africa. However, it is not as effective as antimalarial prophylactic regimens. Therefore, HIV-infected travelers **should not** rely on TMP-SMX for prophylaxis against malaria (**AIII**).

Treating Malaria

- Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infection should be admitted to the hospital for evaluation, initiation of treatment and observation of response to therapy (**AIII**).
- When suspicion of malaria is low, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations.
- Treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed (**AIII**).
- When malaria is strongly suspected, but not yet confirmed, clinicians are advised to consider and initiate treatment for other possible diagnoses in addition to malaria.
- Treatment recommendations for HIV-infected patients are the same as HIV-uninfected patients (**AIII**).
- Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, and the likely drug susceptibility of the infected species.
- For treatment recommendations for specific region, clinicians should refer to
 - The CDC malaria website: <http://www.cdc.gov/malaria/>
 - The CDC Malaria Hotline: (770) 488-7788; Monday through Friday, 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours.

Key to Acronyms: CDC = the Centers for Disease Control and Prevention; TMP-SMX = Trimethoprim-sulfamethoxazole

References:

1. World Health Organization. 2008 World Malaria Report. Available at <http://www.who.int/malaria/publications/atoz/9789241563697/en/index.html>. Accessed March 14, 2013.
2. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*. Jun 28 2001;344(26):1973-1978. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11430326>.
3. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. *JAMA*. Jul 22-29 1992;268(4):516-519. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1619744>.
4. Centers for Disease C. Update: self-induced malaria associated with malariotherapy for Lyme disease--Texas. *MMWR Morb Mortal Wkly Rep*. Oct 4 1991;40(39):665-666. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1896006>.
5. Mali S, Steele S, Slutsker L, Arquin PM, Centers for Disease C, Prevention. Malaria surveillance - United States, 2008. *MMWR Surveill Summ*. Jun 25 2010;59(7):1-15. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20577158>.
6. Guerra CA, Howes RE, Patil AP, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. *PLoS Negl Trop Dis*. 2010;4(8):e774. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20689816>.
7. Korenromp EL, Williams BG, de Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis*. Sep 2005;11(9):1410-1419. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16229771>.
8. Van Geertruyden JP, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. *Malar J*. 2008;7:134. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18647387>.
9. Slutsker L, Marston BJ. HIV and malaria: interactions and implications. *Curr Opin Infect Dis*. Feb 2007;20(1):3-10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17197875>.
10. Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of Travel of Adults Infected with HIV. *J Travel Med*. Jun 1 1995;2(2):85-88. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9815367>.
11. Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel*

- Med.* Jun 1999;6(2):71-75. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10381957>.
12. Castelli F, Patroni A. The human immunodeficiency virus-infected traveler. *Clin Infect Dis.* Dec 2000;31(6):1403-1408. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11096010>.
 13. Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. *Am J Med.* Jul 2007;120(7):574-580. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17602926>.
 14. Smego RA, Jr. Effectiveness of antimalarial drugs. *N Engl J Med.* Jul 28 2005;353(4):420-422; author reply 420-422. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16050053>.
 15. Suh KN, Mileno MD. Challenging scenarios in a travel clinic: advising the complex traveler. *Infect Dis Clin North Am.* Mar 2005;19(1):15-47. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15701545>.
 16. Sherrard AW, McCarthy AE. Travel patterns and health risks for patients infected with HIV. *Travel Med Infect Dis.* Sep 2009;7(5):291-295. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19747664>.
 17. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med.* Aug 15 2002;347(7):505-516. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12181406>.
 18. Spira AM. Assessment of travellers who return home ill. *Lancet.* Apr 26 2003;361(9367):1459-1469. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12727414>.
 19. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis.* Jul 1987;156(1):84-91. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3598228>.
 20. Winer L, Alkan M. Incidence and precipitating factors of morbidity among Israeli travelers abroad. *J Travel Med.* Sep-Oct 2002;9(5):227-232. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12962594>.
 21. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis.* Jun 15 2007;44(12):1560-1568. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17516399>.
 22. Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. *Science.* May 14 2010;328(5980):866-871. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20466925>.
 23. Snow RW, Marsh K. The consequences of reducing transmission of *Plasmodium falciparum* in Africa. *Advances in parasitology.* 2002;52:235-264. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12521262>.
 24. Matteelli A, Casalini C, Bussi G, et al. Imported malaria in an HIV-positive traveler: a case report with a fatal outcome. *J Travel Med.* Jul-Aug 2005;12(4):222-224. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16086898>.
 25. Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and laboratory features of human *Plasmodium knowlesi* infection. *Clin Infect Dis.* Sep 15 2009;49(6):852-860. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19635025>.
 26. Severe and complicated malaria. World Health Organization, Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg.* 1990;84 Suppl 2(Suppl 2):1-65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2219249>.
 27. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bulletin of the World Health Organization.* 1989;67(2):189-196. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2743538>.
 28. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *The Quarterly journal of medicine.* May 1989;71(265):441-459. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2690177>.
 29. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. *QJM: monthly journal of the Association of Physicians.* Apr 1997;90(4):263-270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9307760>.
 30. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med.* May 25 1995;332(21):1399-1404. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7723795>.
 31. Cox-Singh J, Davis TM, Lee KS, et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis.* Jan 15 2008;46(2):165-171. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18171245>.
 32. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet.* Sep 23 2000;356(9235):1051-1056. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11009139>.
 33. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis.* Sep 15 2005;192(6):984-991. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16107950>.

34. Mouala C, Guiguet M, Houze S, et al. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS*. Sep 24 2009;23(15):1997-2004. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19654499>.
35. Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. *J Infect Dis*. Mar 15 2006;193(6):872-878. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16479522>.
36. Cohen C, Karstaedt A, Freaun J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis*. Dec 1 2005;41(11):1631-1637. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16267737>.
37. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS*. Feb 20 2004;18(3):547-554. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15090809>.
38. Tkachuk AN, Moormann AM, Poore JA, et al. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. *J Infect Dis*. Mar 15 2001;183(6):967-972. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11237815>.
39. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS*. Apr 30 2004;18(7):1051-1059. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15096809>.
40. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. *AIDS*. Nov 21 2003;17(17):2539-2541. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14600529>.
41. Inion I, Mwanyumba F, Gaillard P, et al. Placental malaria and perinatal transmission of human immunodeficiency virus type 1. *J Infect Dis*. Dec 1 2003;188(11):1675-1678. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14639538>.
42. Ayisi JG, van Eijk AM, Newman RD, et al. Maternal malaria and perinatal HIV transmission, western Kenya. *Emerg Infect Dis*. Apr 2004;10(4):643-652. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15200854>.
43. 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>.
44. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet*. Apr 15 2006;367(9518):1256-1261. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16631881>.
45. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS*. Jul 1 2005;19(10):995-1005. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15958830>.
46. Katrak S, Gasasira A, Arinaitwe E, et al. Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperazine for malaria in young HIV-infected and uninfected children. *Malar J*. 2009;8:272. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19948038>.
47. Gasasira AF, Kanya MR, Achan J, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. Apr 1 2008;46(7):985-991. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18444813>.
48. Parikh S, Gut J, Istvan E, Goldberg DE, Havlir DV, Rosenthal PJ. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrob Agents Chemother*. Jul 2005;49(7):2983-2985. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15980379>.
49. Van Geertruyden JP, Mulenga M, Mwananyanda L, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. *J Infect Dis*. Oct 1 2006;194(7):917-925. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16960779>.
50. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. Feb 2007;7(2):93-104. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17251080>.
51. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment of malaria in the United States: a systematic review. *JAMA*. May 23 2007;297(20):2264-2277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17519416>.
52. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. *Trans R Soc Trop Med Hyg*. Mar-Apr 2002;96(2):180-184. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12055810>.
53. Centers for Disease Control and Prevention. Update: New Recommendations for Mefloquine Use in Pregnancy. http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html. Accessed March 14, 2013. 2011.

Penicilliosis marneffeii (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffeii*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.¹⁻³ More recently, indigenous cases of penicilliosis have been seen in several states of India, particularly Manipur, which is a new endemic area for this fungus.⁴⁻⁶

Before the era of antiretroviral therapy (ART), penicilliosis was the presenting AIDS-defining illness in 6.8% of HIV-infected patients from the northern provinces of Thailand and less common elsewhere.⁷ Most cases of penicilliosis are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm³.⁸ The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered.⁹

No data are available on acquisition and transmission of penicilliosis. However, like histoplasmosis, it is believed to be acquired by inhalation of microconidia from the mycelial phase of the organism. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and it is the presumed mechanism for disease occurrence in nonendemic areas. Evidence exists for seasonality in penicilliosis infections; increased cases have been noted during the rainy months.^{10,11}

Clinical Manifestations

The common clinical manifestations include fever, anemia, weight loss, and generalized skin papules with central umbilication resembling molluscum contagiosum.^{1,5} Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs, such as the central nervous system, bone marrow, lymph node, lung, liver, and intestine, has been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels.³

Diagnosis

The definitive diagnosis of penicilliosis is based on isolation of organisms from cultures of blood or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. *P. marneffeii* exhibits dimorphic growth in culture. At 25°C, the fungus grows as a mold, demonstrating characteristic colonies that include a flat green surface and underlying deep red coloring. At 37°C the fungus grows as white colonies of yeast.¹²

An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffeii*.^{1,5} In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.¹³

Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting endemic areas, and particularly rural areas in those regions (BIII).

Preventing Disease

A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole, 200 mg daily for primary prophylaxis, significantly reduced occurrence of systemic fungal infections (cryptococcosis and penicilliosis) in HIV-infected patients with CD4 counts <200 cells/mm³.⁸ Fluconazole

may also be effective prophylaxis.¹⁴ For most patients from the United States, such primary prophylaxis would only be indicated in unusual situations in which those who are highly immunosuppressed have to travel to high-risk areas.

Indication for Primary Prophylaxis

All HIV-infected patients with CD4 counts <100 cells/mm³ who reside or stay for a long period in northern Thailand, Vietnam, and southern China, and particularly in rural areas, should be administered primary prophylaxis (**BI**). The preferred drug for prophylaxis is oral itraconazole, 200 mg/day (**BI**). An alternative drug is oral fluconazole 400 mg once weekly (**BII**). Primary prophylaxis is not indicated in other geographic areas.¹⁵

Discontinuation of Primary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of primary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse in penicilliosis and invasive fungal infections after discontinuation of itraconazole in patients receiving ART who had CD4 counts >100 cells/mm³.¹⁶ Therefore, primary prophylaxis for penicilliosis can logically be discontinued in AIDS patients who receive combination ART and have CD4 counts >100 cells/mm³ for ≥ 6 months but there are no convincing data addressing this issue (**CII**). Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm³ (**BIII**).

Treating Disease

The recommended treatment is liposomal amphotericin B, 3 to 5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks (**AII**), followed by secondary prophylaxis.¹⁷ Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (**BII**),¹⁸ followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal. Itraconazole oral solution can be taken on an empty stomach.

The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks (**BII**).¹⁹ The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.

Special Considerations with Regard to Starting ART

No studies exist regarding the optimal time to start ART in HIV-infected patients with acute penicilliosis, but anecdotal experience and information from clinical trials on other HIV associated opportunistic infections suggests that in those with active penicilliosis who have CD4 counts ≤ 50 cells/mm³, ART should be started as soon as possible after the initiation of antifungal therapy (**BIII**). In patients with CD4 counts >50 cells/mm³, it may be prudent to delay initiation of ART until after completion of the first 2 weeks of induction therapy for penicilliosis (**CIII**).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline reduces the risk of nephrotoxicity during treatment (**BII**). Infusion-related adverse reactions can be ameliorated by pretreatment with acetaminophen and diphenhydramine.

Because absorption of itraconazole can be erratic and because itraconazole can interact with some antiretroviral drugs, serum itraconazole levels should be obtained in all patients to ensure adequate drug exposure (**AIII**). The serum concentration should be >1 $\mu\text{g/mL}$. Itraconazole solution is recommended over the capsule formulation because of better bioavailability, but this has not been studied specifically in AIDS patients.

Azoles and antiretroviral drugs such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) do interact (see [Table 5](#)). Through the CYP3A4 mechanism, itraconazole and voriconazole can increase blood levels and effects of PIs and NNRTIs. On the other hand, NNRTIs can slightly decrease blood levels of itraconazole and voriconazole. Close monitoring should be done when using these drugs together.

The unmasking type of immune reconstitution inflammatory syndrome (IRIS) has been reported in several patients with penicilliosis.^{20,21} No paradoxical IRIS responses have been reported when ART is initiated in patients with established penicilliosis. ART should not be withheld because of concern for possible development of IRIS (**AIII**).

Managing Treatment Failure

Voriconazole has been reported to have good outcomes and can be used in patients whose infections fail to respond to initial therapy with amphotericin B followed by itraconazole (**BII**).¹⁹

Preventing Recurrence

When To Start Secondary Prophylaxis

A study showed that more than 50% of patients not treated with ART had relapse of *P. marneffei* within 6 months after discontinuation of antifungal therapy.^{18,22} A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients, reduced the relapse rate for *P. marneffei* from 57% to 0% ($P < 0.001$).²² All patients who successfully complete treatment for penicilliosis should receive secondary prophylaxis (chronic maintenance therapy) with oral itraconazole 200 mg/day (**AI**) and should be started on ART if that was not done during acute disease (**AIII**).

When To Stop Secondary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse of penicilliosis after discontinuation of itraconazole in patients receiving ART whose CD4 cell counts were >100 cells/mm³.¹⁶ Therefore, secondary prophylaxis for penicilliosis can be discontinued in AIDS patients who receive combination ART and have CD4 cell counts >100 cells/mm³ for at least 6 months (**BII**). Secondary prophylaxis should be reintroduced if the CD4 cell count decreases to <100 cells/mm³ (**AIII**).

Special Considerations During Pregnancy

Diagnosis and treatment of penicilliosis during pregnancy are similar to those in non-pregnant adults, with the following considerations regarding antifungal use in pregnancy. Amphotericin B has not been shown to be teratogenic in animals, and no increase in anomalies has been seen with its use in humans. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so the data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited.

Voriconazole is Food and Drug Administration category D because of cleft palate and renal defects seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended. No evidence of birth defects has been seen after episodic exposure to single, 150-mg doses of fluconazole. With chronic use of doses ≥ 400 mg in pregnancy, however, 5 cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported (fluconazole embryopathy).²³

Substitution of amphotericin B for high-dose azoles in the first trimester is recommended (**BIII**). Women on secondary prophylaxis with itraconazole or other azoles should postpone pregnancy until their CD4 cell counts have been restored with ART, such that prophylaxis can be discontinued (**BIII**).

Recommendations for Preventing and Treating *Penicillium marneffe* Infection

Preventing 1st Episode of Penicilliosis (Primary Prophylaxis)

Indication for Primary Prophylaxis:

- Patients with CD4 count <100 cells/mm³ who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas **(BI)**

Preferred Therapy:

- Itraconazole^a 200 mg PO once daily **(BI)**

Alternative Therapy:

- Fluconazole 400 mg PO once weekly **(BII)**

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >100 cells/mm³ for ≥ 6 months in response to ART **(CII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count decreases to <100 cells/mm³ **(BIII)**

Treating Acute Infection in Severely Ill Patients

Preferred Therapy:

- Liposomal amphotericin B, 3 to 5 mg/kg/day IV for 2 weeks; followed by itraconazole^a 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy **(AII)**

Alternative Therapy:

- Voriconazole^a 6 mg/kg IV q12h for 1 day, then 4 mg/kg q12h for at least 3 days, followed by voriconazole^a 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy **(BII)**

Treating Mild Disease

Preferred Therapy:

- Itraconazole^a 200 mg PO BID for 8 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

Alternative Therapy:

- Voriconazole^a 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Itraconazole^a 200 mg PO daily **(AI)**

Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count >100 cells/mm³ for ≥ 6 months in response to ART **(BII)**

Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count <100 cells/mm³ **(AIII)**, or
- If penicilliosis recurs at CD4 count >100 cells/mm³ **(CIII)**

Other Considerations:

- ART should be administered simultaneously with treatment for penicilliosis to improve outcome. **(CIII)**
- Because of the erratic absorption and potential for drug interactions with ARV therapy, itraconazole concentration should be monitored, and serum concentration should be > 1 mcg/mL.

^a Both itraconazole and voriconazole can have significant drug-drug interactions with various ARV drugs, dosage adjustment may be necessary, consider therapeutic drug monitoring to guide therapy. See [Table 5](#) for drug interaction information

Key to Acronyms: CD4 = CD4 T lymphocyte; PO = orally; IV = intravenous; q(n)h = every “n” hours; BID = twice daily; ART = antiretroviral therapy, ARV = antiretroviral

References

1. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in southeast Asia. *Lancet*. Jul 9 1994;344(8915):110-113. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7912350>.
2. Clezy K, Sirisanthana T, Sirisanthana V, Brew B, Cooper DA. Late manifestations of HIV in Asia and the Pacific. *AIDS*. 1994;8 Suppl 2(Suppl 2):S35-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7857567>.
3. Kantipong P, Panich V, Pongsurachet V, Watt G. Hepatic penicilliosis in patients without skin lesions. *Clin Infect Dis*. May 1998;26(5):1215-1217. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9597255>.
4. Singh PN, Ranjana K, Singh YI, et al. Indigenous disseminated *Penicillium marneffei* infection in the state of Manipur, India: report of four autochthonous cases. *J Clin Microbiol*. Aug 1999;37(8):2699-2702. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10405425>.
5. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated *Penicillium marneffei* infection among HIV-infected patients in Manipur state, India. *J Infect*. Nov 2002;45(4):268-271. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12423616>.
6. Devi SB, Devi TS, Ningshen R, Devi Kh R, Singh TB, Singh NB. *Penicillium morneffei*, an emerging AIDS-related pathogen—a RIMS study. *J Indian Med Assoc*. Apr 2009;107(4):208-210. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19810362>.
7. Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE. Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: regional variation and temporal trends. *Clin Infect Dis*. Mar 15 2001;32(6):955-962. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11247718>.
8. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clin Infect Dis*. Jan 15 2002;34(2):277-284. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11740718>.
9. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated *Penicillium marneffei* infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. Nov 1993;37(11):2407-2411. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8285625>.
10. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. Jun 1996;173(6):1490-1493. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8648227>.
11. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated *Penicillium marneffei* infection in Ho Chi Minh City, Viet Nam. *Clin Infect Dis*. Apr 1 2011;52(7):945-952. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21427403>.
12. Vanittanakom N, Cooper CR, Jr., Fisher MC, Sirisanthana T. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. Jan 2006;19(1):95-110. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16418525>.
13. Supparatpinyo K, Sirisanthana T. Disseminated *Penicillium marneffei* infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. Feb 1994;18(2):246-247. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8161635>.
14. Chaiwarith R, Fakhongyoo A, Preparattanapan J, Boonmee D, Sirisanthana T, Supparatpinyo K. Itraconazole vs fluconazole as a primary prophylaxis for fungal infections in HIV-infected patients in Thailand. *Curr HIV Res*. Jul 2011;9(5):334-338. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21916838>.
15. Hilmarisdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated *Penicillium marneffei* infection in a patient with AIDS. *Clin Infect Dis*. Aug 1994;19(2):357-358. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7986922>.
16. Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis *marneffei* in AIDS patients after HAART. *AIDS*. Jan 30 2007;21(3):365-367. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17255744>.
17. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. *Clin Infect Dis*. May 1998;26(5):1107-1110. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9597237>.

18. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al. An efficacy study of itraconazole in the treatment of *Penicillium marneffei* infection. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. Dec 1992;75(12):688-691. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1339213>.
19. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic *Penicillium marneffei* infections in AIDS patients. *Am J Trop Med Hyg*. Aug 2007;77(2):350-353. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17690411>.
20. Manosuthi W, Chaovavanich A, Tansuphaswadikul S, et al. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. *J Infect*. Nov 2007;55(5):464-469. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17714788>.
21. Gupta S, Mathur P, Maskey D, Wig N, Singh S. Immune restoration syndrome with disseminated *Penicillium marneffei* and cytomegalovirus co-infections in an AIDS patient. *AIDS Res Ther*. 2007;4:21. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17922912>.
22. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. *N Engl J Med*. Dec 10 1998;339(24):1739-1743. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9845708>.
23. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. Birth defects research. Part A, *Clinical and molecular teratology*. Nov 2005;73(11):919-923. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16265639>.

Epidemiology

Leishmaniasis is caused by obligate intracellular protozoa that survive and replicate in intracellular vacuoles within macrophages and other mononuclear cells. The *Leishmania* genus has traditionally been differentiated into multiple species that cause cutaneous, mucosal, and/or visceral disease.^{1,2}

Leishmaniasis occurs in 98 countries or territories in the tropics, subtropics, and southern Europe with an estimated incidence of 1.5 million new cases annually—as many as 1.2 million cases of cutaneous leishmaniasis and 0.4 million cases of visceral leishmaniasis.³ As of March 2010, HIV-leishmaniasis co-infection has been reported in 35 countries, predominantly as visceral leishmaniasis.^{3,4} The first cases of HIV-leishmaniasis co-infection were described in Spain in the late 1980s. During the 1980s and 1990s, more than 90% of co-infection cases were reported in southern Europe.^{3,5} After the introduction of combination antiretroviral therapy (ART), the incidence has decreased substantially in developed countries,^{6,7} but HIV-leishmaniasis co-infection poses a growing problem in parts of Asia, Africa, and Latin America.^{3,4,8,9} In one large leishmaniasis specialty hospital in Bihar, India, the prevalence of HIV infection in patients with visceral leishmaniasis has increased from 0.88% in 2000 to 2.18% in 2006.³ In a study in a treatment center in Humera in northwestern Ethiopia, 31% of patients with visceral leishmaniasis were co-infected with HIV.¹⁰ Most leishmanial infections in immunocompetent hosts are asymptomatic. In many disease-endemic areas, 30% or more of the population has evidence of latent infection, as demonstrated by a positive leishmanin skin test.¹¹⁻¹³ After primary infection, *Leishmania* remain viable in healthy individuals for long periods, leading to a population at risk of reactivation if immunosuppression occurs. In HIV-infected patients without severe immunosuppression, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 T lymphocyte (CD4) cell count <200 cells/mm³), manifestations of leishmaniasis can be both atypical and more severe, and relapse after treatment—especially of visceral leishmaniasis—is common.^{14,15}

In endemic areas, Leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*.² However, in Southern Europe, HIV and *Leishmania infantum* visceral co-infections were reported in association with injection-drug use, suggesting that *Leishmania* also may be acquired by needle sharing.¹⁶ *Leishmania* parasites were demonstrated in 34% to 52% of used syringes discarded by injection-drug users in Madrid, and, based on molecular characteristics, investigators have described a new, epidemiologically significant leishmaniasis transmission cycle, relying on mechanical transfer of amastigotes via syringe.^{17,18}

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous and visceral leishmaniasis, but also related syndromes, such as mucosal (or mucocutaneous) leishmaniasis, disseminated cutaneous leishmaniasis, diffuse cutaneous leishmaniasis (an anergic form), and post-kala-azar dermal leishmaniasis. The most common clinical presentation of leishmaniasis in HIV-infected individuals is a systemic visceral disease syndrome, but the distribution varies geographically, reflecting differences in the predominant parasite species. In Europe, visceral disease has been reported in 95% of cases (87% typical visceral, 8% atypical visceral).^{4,5} In contrast, in Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported cases, respectively.¹⁹

In patients with HIV and visceral disease, the most common clinical and laboratory findings are fever (65%–100%), systemic malaise (70%–90%), splenomegaly (usually moderate) (60%–90%), hepatomegaly without splenomegaly (34%–85%), hepatosplenomegaly (68%–73%), lymphadenopathy (12%–57%), and pancytopenia (50%–80%).^{5,15} Anemia is usually marked, with <10g hemoglobin/dL (49%–100%); leukopenia moderate, with <2400 leukocytes/ μ L (56%–95%); and thrombocytopenia usually is present

(52%–93%). Splenomegaly is less pronounced in HIV-co-infected patients than in immunocompetent patients with visceral leishmaniasis.¹⁵ In those with more profound immunosuppression, atypical manifestations have been described, including involvement of the upper and lower gastrointestinal tract, lung, pleural and peritoneal cavities, and skin.^{4-6,15,20} Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis.⁵ Non-ulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described.²¹⁻²³ However, the presence of *Leishmania* amastigotes in skin can occur in the absence of lesions or in combination with other pathology, such as KS, and does not prove that the parasite is the cause of the lesions.^{24,25}

Disfiguring mucosal lesions associated with anergy to *Leishmania* antigens have been observed in Europeans with AIDS, in contrast to mucocutaneous disease in immunocompetent patients, which is associated with strong leishmanin skin-test responses.^{20,26,27}

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, and smears in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in HIV-co-infected patients.^{4,5}

Visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in blood smears (approximately 50% sensitivity in expert hands), buffy-coat smear preparations, cultures from the peripheral blood, and smears or cultures from bone marrow or splenic aspirates. Other methods useful for demonstrating *Leishmania* in the blood or tissue of co-infected patients include detection of *Leishmania* nucleic acid by PCR amplification (>95% sensitivity).¹⁸

Serologic tests to detect antibodies against *Leishmania* antigens have high sensitivity to diagnose visceral leishmaniasis in immunocompetent patients.²⁸ Serology should not be used as a screening test as positive serology can occur in individuals with asymptomatic infection. It should be used only as a confirmatory test in patients with a compatible clinical picture and exposure history suggestive of visceral leishmaniasis. Serology has a low sensitivity in HIV-infected patients, especially in Europe, such that parasitological diagnosis should be sought when clinical suspicion has been raised.^{4,5,29}

The use of recombinant antigen in ELISA assays may increase sensitivity, but a proportion of co-infected patients remain seronegative.³⁰ Immunoblotting with *Leishmania infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of European patients.²⁹ Interestingly, reports suggest that the serology sensitivity may remain fairly high in HIV-co-infected patients in Ethiopia (77%–89% in HIV-visceral leishmaniasis co-infected patients, versus 87%–95% in HIV-negative patients).³¹ Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV co-infection.²

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in areas with zoonotic transmission and vector control activities, such as indoor residual spraying and/or use of insecticide-treated bed nets. The best way for travelers to leishmaniasis-endemic areas to prevent infection is to protect themselves from sand fly bites. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin.

Measures to decrease transmission of infectious agents in injection-drug users, such as the use of needle exchange programs, are appropriate.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended, and no screening or preemptive

therapy is appropriate for HIV-infected patients who may have been exposed to leishmanial infection. No vaccine against leishmaniasis is available.

Treating Disease

Visceral Leishmaniasis

For HIV-infected patients with visceral leishmaniasis, conventional and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.^{4,32-35} Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than conventional amphotericin B (amphotericin B deoxycholate) or pentavalent antimony (sodium stibogluconate).³⁶⁻³⁸ The equivalent efficacy and better toxicity profile have led most clinicians to regard liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-co-infected patients (**AII**).^{4,39} The optimal amphotericin B dosage has not been determined.^{39,40} Regimens with efficacy include liposomal preparations of 2 to 4 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight (**AII**), or amphotericin B deoxycholate, 0.5 to 1.0 mg/kg body weight/day intravenously (IV), to achieve a total dose of 1.5 to 2.0 g (**BII**).^{32,35,39,41-43} Pentavalent antimony (sodium stibogluconate), which is available in the United States through the Centers for Disease Control and Prevention (CDC), 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, may be considered as an alternative (**BII**).

Additional treatment options for visceral leishmaniasis in HIV-co-infected patients include oral miltefosine and parenteral paromomycin. Miltefosine is an oral antileishmanial agent currently available outside the United States and may be used under individual investigational new drug protocols in the United States. Consultations and drug requests should be addressed to CDC Parasitic Diseases Inquiries (404-718-4745; parasites@cdc.gov), the CDC Drug Service (404-639-3670; drugservice@cdc.gov), and; for emergencies after business hours, on weekends, and federal holidays; through the CDC Emergency Operations Center (770-488-7100).

Cure rates for visceral leishmaniasis in HIV-negative patients are reported to be approximately 95%.⁴⁴ In Ethiopia, HIV-co-infected patients treated with miltefosine had lower initial cure rates, compared with those treated with pentavalent antimony (sodium stibogluconate) (78% vs. 90%), but also lower mortality.⁴⁵ The adult dose is 100 mg daily for 4 weeks. Data supporting the use of miltefosine in HIV-co-infected patients are limited, but it can be used for treatment of visceral leishmaniasis in Europe under a compassionate use protocol (**CIII**).⁴⁶ Gastrointestinal symptoms are common but they rarely limit treatment. Paromomycin, an aminoglycoside which is available outside the United States, has been shown to be used successfully in a small number of HIV-negative visceral leishmaniasis patients in India and is now in use in several countries.⁴⁰ No efficacy data currently are available for paromomycin in HIV-co-infected patients. A recent trial of combination therapy (liposomal amphotericin plus miltefosine or paromomycin; miltefosine plus paromomycin) produced promising results in patients in India whose visceral leishmaniasis was not severe.⁴⁷ Further research is needed to validate the efficacy of these regimens in severe disease in visceral leishmaniasis in other geographic regions, and in HIV-co-infected patients.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous, mucocutaneous, or diffuse cutaneous leishmaniasis in HIV-co-infected patients. On the basis of data in HIV-negative patients with cutaneous leishmaniasis and case reports in HIV-co-infected patients, HIV-infected patients should be treated with liposomal amphotericin B (**BIII**), as previously outlined,⁴⁸ or pentavalent antimony (sodium stibogluconate), depending on the form of the disease and the clinical response (**BIII**).^{2,49,50} However, pentavalent antimony can increase viral transcription and HIV replication in cultures of human peripheral blood mononuclear cells, raising concerns about its use in HIV-infected patients.⁵¹

Potential alternatives for cutaneous leishmaniasis include miltefosine, topical paromomycin, intralesional

pentavalent antimony, and local heat therapy; however, no data exist for co-infected patients and in immunocompetent patients, the effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.^{40,52-54}

Special Considerations with Regard to Starting ART

ART should be initiated or optimized following standard practice for HIV-infected patients (**AIII**). There are no leishmaniasis-specific data on when to start ART. Appropriate use of ART has substantially improved the survival of co-infected patients in Europe and decreases the likelihood of relapse after antileishmanial therapy.^{7,15,55} Therefore, ART should be started as soon as patients are able to tolerate it (**AIII**).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients treated with liposomal amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions (**AII**). Infusional adverse events are ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids (**BII**). Infusion of 1 L of saline over an hour before drug infusion can help reduce the risk of glomerular function decline during treatment (**BIII**). The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for amphotericin B deoxycholate.³⁷ Amphotericin B deoxycholate treatment is also associated with an increased risk of anemia.³³

Patients receiving pentavalent antimony (sodium stibogluconate) should be monitored closely for adverse reactions.⁴⁹ Overall, at a dose of 20 mg/kg of body weight per day, greater than 60% of patients have 1 or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and (in some patients) clinical pancreatitis. Weekly electrocardiograms are recommended during treatment, with vigilance for changes that may indicate early cardiotoxicity, such as prolonged QT intervals and T-wave inversion (**CIII**). Rarely, arrhythmias and sudden death have occurred.^{33,41} Severe adverse reactions to pentavalent antimony (sodium stibogluconate), including acute pancreatitis and leukopenia, appear to be more common in co-infected patients than in those who are not infected with HIV.⁵⁶

Cases of newly symptomatic visceral and cutaneous leishmaniasis have been reported in association with the immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.^{57,58} Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.⁵⁹⁻⁶² Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

Managing Treatment Failure

For patients who fail to respond to initial therapy or experience a relapse after initial treatment, a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy should be used, as previously outlined (**AIII**). The response rate for retreatment appears to be similar to that for initial therapy, although some patients evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.

Immunotherapy, including interferon-gamma and recombinant human granulocyte macrophage colony stimulating factor (GM-CSF), has been used experimentally as an adjunct to antileishmanial treatment for refractory cases.^{63,64} However, a clinical trial of pentavalent antimony (sodium stibogluconate) plus interferon-gamma for visceral leishmaniasis in HIV-co-infected patients was suspended when an interim analysis indicated that there was no advantage over pentavalent antimony (sodium stibogluconate) alone.⁴¹ In addition, the use of interferon-gamma was reported to be associated with acceleration of KS in two patients with visceral leishmaniasis and HIV co-infection.²⁴

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of anti-leishmanial therapy in HIV-infected patients, and frequency of relapse is inversely related to CD4 cell count. In HIV-co-infected patients with visceral leishmaniasis who were not receiving or responding to ART, the risk of relapse at 6 and 12 months was 60% and 90%, respectively, in the absence of secondary prophylaxis (chronic maintenance therapy).^{5,65} Therefore, secondary prophylaxis with an effective antileishmanial drug, administered at least every 2 to 4 weeks, is recommended, particularly for patients with visceral leishmaniasis and CD4 cell counts <200 cells/ μ L (**AII**).^{5,15,34,65}

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex (3 mg/kg every 21 days) in 8 patients to no prophylaxis in 9 patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.³⁴ In retrospective observational studies, monthly pentavalent antimony (sodium stibogluconate) or lipid formulations of amphotericin every 2 to 4 weeks were also associated with decreased relapse rates.^{15,65} Liposomal amphotericin B (4 mg/kg every 2–4 weeks) or amphotericin B lipid complex (3 mg/kg every 21 days) should be used for secondary prophylaxis (**AII**). Pentavalent antimony (sodium stibogluconate), 20 mg/kg IV or IM every 4 weeks, is an alternative (**BII**). Although pentamidine is no longer recommended to treat primary visceral leishmaniasis, it has been suggested as another alternative for secondary prophylaxis in a dosage of 6 mg/kg IV every 2 to 4 weeks (**CIII**).⁶⁶ Allopurinol, in a dose of 300 mg orally 3 times daily, used for maintenance therapy is less effective than monthly pentavalent antimony and **is not recommended** (**BII**).⁶⁵ Although no published data on efficacy are available, maintenance therapy may be indicated for immunocompromised patients with cutaneous leishmaniasis who have multiple relapses after adequate treatment (**CIII**).

When to Stop Secondary Prophylaxis

Some investigators suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm³ in response to ART.⁶⁷ Others, however, suggest that secondary prophylaxis should be maintained indefinitely. In one study, a positive peripheral blood PCR for *leishmania* correlated with a high risk of relapse.⁶⁸ Thus, because there are so little published data or clinical trial experience, no recommendation can be made regarding discontinuation of secondary prophylaxis in HIV-leishmania-co-infected persons.

Special Considerations During Pregnancy

Diagnostic considerations are the same in pregnant women as in women who are not pregnant. One study suggests that lesions of cutaneous leishmaniasis may be larger and more likely to be exophytic in pregnancy, and that untreated cutaneous leishmaniasis may be associated with an increased risk of preterm delivery and stillbirth.⁶⁹ Labels for pentavalent antimony compounds (sodium stibogluconate, available in the United States through CDC, and meglumine antimoniate) state that these drugs are contraindicated for use in pregnant women, although various antimonial compounds were not teratogenic in chickens, rats, or sheep.⁷⁰⁻⁷² Good clinical and pregnancy outcomes have been reported for small series of pregnant women treated with meglumine antimoniate, amphotericin B deoxycholate, or liposomal amphotericin B.⁷³⁻⁷⁶ Retrospective analyses suggest that rates of preterm birth and spontaneous abortion may be increased in women with visceral leishmaniasis during pregnancy, especially in the first trimester and when antimonial drugs are used.^{77,78} Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy (**AIII**).⁷⁴ The alternatives are amphotericin B deoxycholate (**AIII**) or pentavalent antimony (sodium stibogluconate) (**AIII**). Miltefosine is teratogenic and is contraindicated in pregnancy.⁴⁰ Perinatal transmission of *Leishmania spp.* is rare; 13 documented cases have been reported.^{77,79-81} No data are available on the risk of transmission of *Leishmania spp.* in HIV-infected pregnant women.

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 mg/kg IV daily (**AII**), *or*
- Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) (**AII**)
- Achieve a total dose of 20–60 mg/kg (**AII**)

Alternative Therapy:

- Other amphotericin B lipid complex dosed as above, *or*
- Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams (**BII**), *or*
- Pentavalent antimony (Sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days (**BII**). (Contact the CDC Drug Service at 404-639-3670; drugservice@cdc.gov; for emergencies, call 770-488-7100)
- Miltefosine 100 mg PO daily for 4 weeks (**CIII**). Requires individual IND; consultation should be addressed to CDC Parasitic Diseases Inquiries (404-718-4745; parasites@cdc.gov) or the CDC Drug Service (404-639-3670; drugservice@cdc.gov; for emergencies, call 770-488-7100)

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication:

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm³ (**AII**)

Preferred Therapy:

- Liposomal amphotericin B 4 mg/kg every 2–4 weeks (**AII**), *or*
- Amphotericin B Lipid Complex 3 mg/kg every 21 days (**AII**)

Alternative Therapy:

- Pentavalent antimony (Sodium stibogluconate) 20 mg/kg IV or IM every 4 weeks (**BII**)

Discontinuation of Chronic Maintenance Therapy

Some investigators suggest that therapy can be discontinued after sustained (>3 to 6 months) increase in CD4 count to >200 to 350 cells/mm³ in response to ART, but others suggest that therapy should be continued indefinitely. Therefore, no recommendation can be made regarding discontinuation of chronic maintenance therapy.

Treating Cutaneous Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg (**BIII**), *or*
- Pentavalent antimony (Sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days (**BIII**)

Alternative Therapy:

- Other options include oral miltefosine (can be obtained in the United States through a treatment IND), topical paromomycin, intralésional pentavalent antimony (sodium stibogluconate), or local heat therapy

Chronic Maintenance Therapy for Cutaneous Leishmaniasis

- May be indicated for immunocompromised patients with multiple relapses (**CIII**)

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CDC = the Centers for Disease Control and Prevention; IM = intramuscular; IND = investigational new drug; IV = intravenous

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comparative immunology, microbiology and infectious diseases*. Sep 2004;27(5):305-318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15225981>.
2. Jeronimo SMB, de Queiroz Sousa A, Pearson RD. Leishmaniasis. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical infectious diseases: principles, pathogens and practice*. Edinburgh, Scotland: Churchill Livingstone Elsevier; 2006:1095-1113.

3. World Health Organization. Leishmaniasis. Available at <http://www.who.int/leishmaniasis/burden/en/>. Accessed March 21, 2013.
4. Murray HW. Leishmaniasis in the United States: treatment in 2012. *Am J Trop Med Hyg*. Mar 2012;86(3):434-440. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22403313>.
5. Alvar J, Canavate C, Gutierrez-Solar B, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev*. Apr 1997;10(2):298-319. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9105756>.
6. Rosenthal E, Marty P, del Giudice P, et al. HIV and Leishmania coinfection: a review of 91 cases with focus on atypical locations of Leishmania. *Clin Infect Dis*. Oct 2000;31(4):1093-1095. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11049794>.
7. Tortajada C, Perez-Cuevas B, Moreno A, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. *J Acquir Immune Defic Syndr*. Jul 1 2002;30(3):364-366. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12131576>.
8. Mathur P, Samantaray JC, Vajpayee M, Samanta P. Visceral leishmaniasis/human immunodeficiency virus co-infection in India: the focus of two epidemics. *Journal of medical microbiology*. Jul 2006;55(Pt 7):919-922. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16772420>.
9. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging Leishmania/HIV co-infection in Africa. *Medical microbiology and immunology*. Nov 2001;190(1-2):65-67. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11770113>.
10. ter Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. *Clin Infect Dis*. Jun 1 2008;46(11):1702-1709. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18419422>.
11. Marty P, Le Fichoux Y, Giordana D, Brugnetti A. Leishmanin reaction in the human population of a highly endemic focus of canine leishmaniasis in Alpes-Maritimes, France. *Trans R Soc Trop Med Hyg*. May-Jun 1992;86(3):249-250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1412644>.
12. Moral L, Rubio EM, Moya M. A leishmanin skin test survey in the human population of l'Alacanti region (Spain): implications for the epidemiology of Leishmania infantum infection in southern Europe. *Trans R Soc Trop Med Hyg*. Mar-Apr 2002;96(2):129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12055798>.
13. Werneck GL, Rodrigues L, Santos MV, et al. The burden of Leishmania chagasi infection during an urban outbreak of visceral leishmaniasis in Brazil. *Acta Trop*. Jul 2002;83(1):13-18. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12062788>.
14. Lopez-Velez R, Perez-Molina JA, Guerrero A, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfecting with human immunodeficiency virus and Leishmania in an area of Madrid, Spain. *Am J Trop Med Hyg*. Apr 1998;58(4):436-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9574788>.
15. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. *Medicine (Baltimore)*. Jan 2001;80(1):54-73. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11204503>.
16. Alvar J, Jimenez M. Could infected drug-users be potential Leishmania infantum reservoirs? *AIDS*. Jun 1994;8(6):854. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8086149>.
17. Chicharro C, Morales MA, Serra T, Ares M, Salas A, Alvar J. Molecular epidemiology of Leishmania infantum on the island of Majorca: a comparison of phenotypic and genotypic tools. *Trans R Soc Trop Med Hyg*. Apr 2002;96 Suppl 1:S93-99. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12055859>.
18. Cruz I, Morales MA, Noguera I, Rodriguez A, Alvar J. Leishmania in discarded syringes from intravenous drug users. *Lancet*. Mar 30 2002;359(9312):1124-1125. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11943264>.
19. Rabello A, Orsini M, Disch J. Leishmania/HIV co-infection in Brazil: an appraisal. *Ann Trop Med Parasitol*. Oct 2003;97 Suppl 1:17-28. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14678630>.
20. Mota Sasaki M, Matsumo Carvalho M, Schmitz Ferreira ML, Machado MP. Cutaneous Leishmaniasis Coinfection in AIDS Patients: Case Report and Literature Review. *The Brazilian journal of infectious diseases: an official publication of the Brazilian Society of Infectious Diseases*. Jun 1997;1(3):142-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11105130>.
21. Gonzalez-Beato MJ, Moyano B, Sanchez C, et al. Kaposi's sarcoma-like lesions and other nodules as cutaneous

- involvement in AIDS-related visceral leishmaniasis. *The British journal of dermatology*. Dec 2000;143(6):1316-1318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11122042>.
22. Carnauba D, Jr., Konishi CT, Petri V, Martinez IC, Shimizu L, Pereira-Chiocola VL. Atypical disseminated leishmaniasis similar to post-kala-azar dermal leishmaniasis in a Brazilian AIDS patient infected with *Leishmania (Leishmania) infantum chagasi*: a case report. *Int J Infect Dis*. Nov 2009;13(6):e504-507. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447660>.
 23. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. *The British journal of dermatology*. Feb 2009;160(2):311-318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19187345>.
 24. Albrecht H, Stellbrink HJ, Gross G, Berg B, Helmchen U, Mensing H. Treatment of atypical leishmaniasis with interferon gamma resulting in progression of Kaposi's sarcoma in an AIDS patient. *The Clinical investigator*. Dec 1994;72(12):1041-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7711412>.
 25. Bosch RJ, Rodrigo AB, Sanchez P, de Galvez MV, Herrera E. Presence of *Leishmania* organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral leishmaniasis. *International journal of dermatology*. Oct 2002;41(10):670-675. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12390190>.
 26. Canovas DL, Carbonell J, Torres J, Altes J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. *The Journal of laryngology and otology*. Dec 1994;108(12):1089-1092. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7861090>.
 27. Miralles ES, Nunez M, Hilara Y, Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. *Dermatology*. 1994;189(3):275-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7949483>.
 28. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol*. Sep 2002;9(5):951-958. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12204943>.
 29. Medrano FJ, Canavate C, Leal M, Rey C, Lissen E, Alvar J. The role of serology in the diagnosis and prognosis of visceral leishmaniasis in patients coinfecting with human immunodeficiency virus type-1. *Am J Trop Med Hyg*. Jul 1998;59(1):155-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9684645>.
 30. Houghton RL, Petrescu M, Benson DR, et al. A cloned antigen (recombinant K39) of *Leishmania chagasi* diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. *J Infect Dis*. May 1998;177(5):1339-1344. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9593022>.
 31. ter Horst R, Tefera T, Assefa G, Ebrahim AZ, Davidson RN, Ritmeijer K. Field evaluation of rK39 test and direct agglutination test for diagnosis of visceral leishmaniasis in a population with high prevalence of human immunodeficiency virus in Ethiopia. *Am J Trop Med Hyg*. Jun 2009;80(6):929-934. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19478251>.
 32. Davidson RN, Di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *The Quarterly journal of medicine*. Feb 1994;87(2):75-81. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8153291>.
 33. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS*. Jun 18 1999;13(9):1063-1069. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10397536>.
 34. Lopez-Velez R, Videla S, Marquez M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother*. Mar 2004;53(3):540-543. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14739148>.
 35. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect*. Mar 1996;32(2):133-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8708370>.
 36. Lazanas MC, Tsekas GA, Pappandreou S, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. *AIDS*. Jul 1993;7(7):1018-1019. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8357549>.
 37. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral

- leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis*. Feb 1 2004;38(3):377-383. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14727208>.
38. Torre-Cisneros J, Villanueva JL, Kindelan JM, Jurado R, Sanchez-Guijo P. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. *Clin Infect Dis*. Oct 1993;17(4):625-627. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8268341>.
 39. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis*. Oct 1 2006;43(7):917-924. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16941377>.
 40. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Advances in parasitology*. 2006;61:223-274. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16735166>.
 41. Laguna F, Videla S, Jimenez-Mejias ME, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. *J Antimicrob Chemother*. Sep 2003;52(3):464-468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12888588>.
 42. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis*. Jan 1999;28(1):42-48; discussion 49-51. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10028069>.
 43. Laguna F, Torre-Cisneros J, Moreno V, Villanueva JL, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. Sep 1995;21(3):711-712. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8527591>.
 44. Sundar S, Jha TK, Thakur CP, Bhattacharya SK, Rai M. Oral miltefosine for the treatment of Indian visceral leishmaniasis. *Trans R Soc Trop Med Hyg*. Dec 2006;100 Suppl 1:S26-33. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16730038>.
 45. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis*. Aug 1 2006;43(3):357-364. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16804852>.
 46. Sindermann H, Engel KR, Fischer C, Bommer W, Miltefosine Compassionate Use P. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis*. Nov 15 2004;39(10):1520-1523. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15546090>.
 47. Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet*. Feb 5 2011;377(9764):477-486. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21255828>.
 48. Wortmann G, Zapor M, Ressler R, et al. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg*. Nov 2010;83(5):1028-1033. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21036832>.
 49. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg*. Mar 1992;46(3):296-306. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1313656>.
 50. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis*. Sep 2007;7(9):581-596. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17714672>.
 51. Barat C, Zhao C, Ouellette M, Tremblay MJ. HIV-1 replication is stimulated by sodium stibogluconate, the therapeutic mainstay in the treatment of leishmaniasis. *J Infect Dis*. Jan 15 2007;195(2):236-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17191169>.
 52. Belay AD, Asafa Y, Mesure J, Davidson RN. Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy. *Ann Trop Med Parasitol*. Apr 2006;100(3):223-227. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16630379>.
 53. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis*. Apr 15 2005;40(8):1148-1155. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15791515>.
 54. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis*. May 1 2004;38(9):1266-1272. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15127339>.
 55. de la Rosa R, Pineda JA, Delgado J, et al. Influence of highly active antiretroviral therapy on the outcome of subclinical

- visceral leishmaniasis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. Feb 15 2001;32(4):633-635. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11181128>.
56. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am J Trop Med Hyg*. Nov 1999;61(5):766-769. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10586909>.
 57. Berry A, Abraham B, Dereure J, Pinzani V, Bastien P, Reynes J. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. *Scandinavian journal of infectious diseases*. 2004;36(3):225-227. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15119371>.
 58. Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. *J Infect Dis*. Nov 15 2005;192(10):1819-1822. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16235183>.
 59. Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, et al. Tegumentary leishmaniasis as the cause of immune reconstitution inflammatory syndrome in a patient co-infected with human immunodeficiency virus and *Leishmania guyanensis*. *Am J Trop Med Hyg*. Oct 2009;81(4):559-564. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19815866>.
 60. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *International journal of dermatology*. Dec 2008;47(12):1263-1270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19126013>.
 61. Tadesse A, Hurissa Z. Leishmaniasis (PKDL) as a case of immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patient after initiation of anti-retroviral therapy (ART). *Ethiopian medical journal*. Jan 2009;47(1):77-79. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19743785>.
 62. Antinori S, Longhi E, Bestetti G, et al. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. *The British journal of dermatology*. Nov 2007;157(5):1032-1036. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17854365>.
 63. Badaro R, Johnson WD, Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. *J Infect Dis*. Mar 1993;167 Suppl 1(Suppl 1):S13-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8433014>.
 64. Badaro R, Nascimento C, Carvalho JS, et al. Granulocyte-macrophage colony-stimulating factor in combination with pentavalent antimony for the treatment of visceral Leishmaniasis. *Eur J Clin Microbiol Infect Dis*. 1994;13 Suppl 2:S23-28. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7875148>.
 65. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. *Am J Med*. May 1996;100(5):496-501. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8644760>.
 66. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Tropical medicine & international health: TM & IH*. Sep 2009;14(9):1064-1070. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19552658>.
 67. Berenguer J, Cosin J, Miralles P, Lopez JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. *AIDS*. Dec 22 2000;14(18):2946-2948. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11153679>.
 68. Bourgeois N, Bastien P, Reynes J, Makinson A, Rouanet I, Lachaud L. 'Active chronic visceral leishmaniasis' in HIV-1-infected patients demonstrated by biological and clinical long-term follow-up of 10 patients. *HIV Med*. Nov 2010;11(10):670-673. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20500233>.
 69. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis*. Aug 15 2007;45(4):478-482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17638198>.
 70. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. *American journal of veterinary research*. Jan 1966;27(116):132-135. Available at <http://www.ncbi.nlm.nih.gov/pubmed/5913019>.
 71. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. *Annals of the New York Academy of Sciences*. Aug 8 1952;55(2):203-215. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/12977037>.

72. Rossi F, Acampora R, Vacca C, et al. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. *Teratogenesis, carcinogenesis, and mutagenesis*. 1987;7(5):491-496. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2893463>.
73. Gradoni L, Gaeta GB, Pellizzer G, Maisto A, Scalone A. Mediterranean visceral leishmaniasis in pregnancy. *Scandinavian journal of infectious diseases*. 1994;26(5):627-629. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7855563>.
74. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother*. Feb 2005;55(2):229-233. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15649998>.
75. Topno RK, Pandey K, Das VN, et al. Visceral leishmaniasis in pregnancy - the role of amphotericin B. *Ann Trop Med Parasitol*. Apr 2008;102(3):267-270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18348781>.
76. Utili R, Rambaldi A, Tripodi MF, Andreana A. Visceral leishmaniasis during pregnancy treated with meglumine antimoniate. *Infection*. May-Jun 1995;23(3):182-183. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7499009>.
77. Adam GK, Abdulla MA, Ahmed AA, Adam I. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. *Int J Gynaecol Obstet*. Dec 2009;107(3):208-210. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19766208>.
78. Mueller M, Balasegaram M, Koummuki Y, Ritmeijer K, Santana MR, Davidson R. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother*. Oct 2006;58(4):811-815. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16916865>.
79. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Loscher T. Congenital visceral leishmaniasis. *Emerg Infect Dis*. Feb 2006;12(2):359-360. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17080586>.
80. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics*. Nov 1999;104(5):e65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10545591>.
81. Zinchuk A, Nadraga A. Congenital visceral leishmaniasis in Ukraine: case report. *Ann Trop Paediatr*. 2010;30(2):161-164. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20522305>.

Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*, and transmitted to humans by infected triatomine bugs, and less commonly by transfusion, organ transplant, from mother to infant, and in rare instances, by ingestion of contaminated food or drink.¹⁻⁴ The hematophagous triatomine vectors defecate during or immediately after feeding on a person. The parasite is present in large numbers in the feces of infected bugs, and enters the human body through the bite wound, or through the intact conjunctiva or other mucous membrane.

Vector-borne transmission occurs only in the Americas, where an estimated 8 to 10 million people have Chagas disease.⁵ Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.⁴ In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America, and large-scale migration has brought infected individuals to cities both within and outside of Latin America.^{4,6,7}

Infected triatomine vectors and *T. cruzi*-infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.⁸⁻¹⁰ However, the risk of vector-borne infection within the United States appears to be very low, probably because of better housing conditions and less efficient vectors.¹¹ *T. cruzi* also can be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.^{12,13} Currently an estimated 90% of the U.S. blood supply is screened.

For these reasons, the vast majority of the estimated 300,000 individuals in the United States with Chagas disease are thought to be immigrants who acquired the infection while living in endemic areas in Latin America.¹⁴ In patients chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (for instance, due to advanced HIV disease) may lead to reactivation disease characterized by parasitemia, associated with increased intracellular parasite replication and lack of immunological control of the infection.¹⁵⁻¹⁷

Clinical Manifestations

The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.^{2,4} If the portal of infection was the conjunctiva, patients may develop the characteristic Romana's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.^{2,4} At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective etiologic treatment, *T. cruzi* infection passes into the chronic phase.^{2,18}

Most patients with chronic *T. cruzi* infection have no signs or symptoms, and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of them will progress to clinically evident Chagas disease, most commonly cardiomyopathy.^{2,18} The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.^{4,19} Over time, the disease may progress to higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, congestive heart failure, ventricular aneurysm, and complete heart block are poor prognostic signs, associated with high rates of short-term mortality, including sudden death.²⁰ Chagas digestive disease is much less common than cardiomyopathy, and seen predominantly in infected patients in parts of Brazil and Bolivia.²¹ Dysphagia is the characteristic symptom of megaesophagus, and prolonged

constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, usually detectable by microscopy, and can occur in the settings of immunosuppressive therapy to prevent transplant rejection and cancer chemotherapy, as well as in HIV-infected patients.^{16,22-26} Even in the absence of symptoms, patients with chronic Chagas disease who are HIV-co-infected have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.²⁵ Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts <200 cells/mm³, a history of prior opportunistic infections, or both.¹⁶

The clinical features of reactivated Chagas disease in patients with HIV infection differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).^{15,16,27,28} The presentation may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of AIDS patients with CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in HIV-infected patients is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.^{16,17} Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation or rapid progression of existing chronic cardiomyopathy.^{16,29} Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach or intestine.^{16,29}

Diagnosis

Most patients infected with Chagas disease, including those in the United States, are in the chronic phase and typically unaware of their infection. Screening for infection in patients with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for HIV-infected patients because of the risk of reactivation disease. Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) are used in parallel to improve the accuracy. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.^{30,31} Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.^{32,33} Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.^{30,34} In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection. The sensitivity is highly variable and depends on patient characteristics as well as PCR primers and methods.^{35,36}

In HIV-infected patients with epidemiologic risk factors for Chagas disease, co-infection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.^{16,26,27} The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than *Toxoplasma* lesions.^{17,27,28} Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells, and less often, in neurons. CSF shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.^{16,17,27,28} In a case series that included 15 HIV and *T. cruzi*-co-infected patients with clinical meningoencephalitis, trypomastigotes were visualized in cerebrospinal fluid (CSF) in 85%.^{15,16,27,28}

A definitive diagnosis of re-activation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF or in blood.¹⁶ Circulating parasites are rarely detected microscopically in

immunocompetent patients with chronic Chagas disease or in HIV-co-infected patients in the absence of reactivation.²⁵ If observed in an HIV-*T. cruzi*-co-infected patient, circulating parasites suggest reactivation and the need for treatment. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.³⁷ In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Centrifugation and microscopic examination of CSF also can be employed for patients with suspected CNS Chagas disease. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods, but takes 2 to 8 weeks to demonstrate parasites.

Conventional PCR is not useful for diagnosing re-activation, because the method can yield a positive result in chronic *T. cruzi* infection in the absence of re-activation.^{35,36} However, quantitative PCR assays (real-time PCR) performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.^{38,39} Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.

Preventing Exposure

Travelers to endemic countries may be at risk for infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings constructed of adobe brick, mud, or thatch.⁴⁰ Because the insects feed at night, individuals who live in or visit Chagas disease-endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.⁴¹

Most blood products in the United States are screened routinely for *T. cruzi* but screening is not universal in the United States or in others areas, including parts of Latin America.⁴²

Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

Clinical manifestations of Chagas disease in HIV-positive patients usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected patients with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.¹⁸ A single course of treatment with benznidazole or nifurtimox can be considered for *T. cruzi*-infected individuals who have not been previously treated and who do not have advanced Chagas cardiomyopathy (**CIII**). However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.^{31,43} Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in co-infected patients (**BIII**). Most symptomatic reactivation cases have occurred in patients who were not taking ART.¹⁶

Treating Disease

Chemotherapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute, early-chronic, and re-activated disease.^{43,44} These drugs have limited efficacy, however, in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole (5 to 8 mg/kg/day for 30 to 60 days) is the initial treatment most commonly recommended (**BIII**). Nifurtimox (8 to 10 mg/kg/day, administered for 90 to 120 days) is an alternative (**CIII**). The duration of therapy with either of these agents has not been studied in patients co-infected with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection, even in patients who receive chemotherapy.^{16,27} Limited data suggest that early recognition and treatment of reactivation may improve prognosis.¹⁶

Neither anti-trypanosomal drug is licensed in the United States; however, the drugs are available from the

CDC Drug Service for use under investigational protocols. Consultations and drug requests should be addressed to Division of Parasitic Diseases and Malaria Public Inquiries line (404-718-4745; parasites@cdc.gov), the CDC Drug Service (404-639-3670), and for emergencies after business hours, on weekends, and federal holidays through the CDC Emergency Operations Center (770-488-7100).

Special Considerations with Regard to Starting ART

As with other parasite infections that localize in the CNS, the decision to initiate ART must be carefully considered in HIV-infected patients with reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease as soon as their CNS disease is clinically stable (AIII).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.⁴⁵ Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

As stated above, no reports are available regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients with *T. cruzi* reactivation who fail to respond or who relapse after initial antitrypanosomal therapy (AIII). A publication documents a single case of a *T. cruzi*-infected patient on immunosuppressive therapy for systemic lupus erythematosus who had a good response to posaconazole after failure of benznidazole treatment; failure of benznidazole and response to posaconazole were documented by real-time PCR assays in serial specimens.⁴⁶ Posaconazole is not currently licensed for use in *T. cruzi* infection, but a clinical trial is underway (NCT01162967 in <http://www.clinicaltrials.gov>).

Preventing Recurrence

Patients with HIV infection are at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection.¹⁶ The drugs are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.⁴³ Because the drugs are toxic and experience with their use in HIV-infected patients is limited, expert advice should be sought.⁴⁴ Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when potent ART is used.

Special Considerations During Pregnancy

As recommended for all individuals with epidemiological risk of Chagas disease, screening of pregnant women who have lived in endemic areas should be considered to identify maternal infection and possible risk of infection in their offspring. In pregnant women in areas where the disease is endemic in Latin America, the seroprevalence of *T. cruzi* infection can be as high as 30%.^{14,47} In the United States, one study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of non-Hispanic women.⁴⁸

From 1% to 10% of infants of *T. cruzi*-infected mothers are born with acute *T. cruzi* infection.^{14,47} Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases. Studies from the 1980s suggest that congenital transmission of *T. cruzi* may increase the risk of spontaneous abortion, stillbirth, and low birthweight.⁴⁹ In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningoencephalitis, and/or

respiratory insufficiency, with high risk of mortality.⁴⁷ Limited data suggest that the rate of congenital transmission is higher for HIV-infected women than in immunocompetent mothers.^{16,50} Infants co-infected with HIV and *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.^{51,52}

Minimal data are available on potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.^{53,54} Benznidazole crosses the placenta in rats and covalently binds to fetal proteins.⁵⁵ Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection in pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy. For HIV-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, ART should be initiated (**AIII**). All infants born to *T. cruzi*-infected women should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.^{14,56}

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Clinical Disease

Indication

- Individuals with epidemic risk factors for Chagas disease and tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy.
 - A single course of benznidazole or nifurtimox can be considered (doses and duration same as for treatment of disease) (**CIII**). However, the efficacy of this therapy is suboptimal, and treated patients are still at risk of reactivation.
 - Initiation or optimization of ART may prevent reactivation of Chagas disease (**BIII**)

Treating Chagas Disease

Note: Treatment is effective in reducing parasitemia and preventing clinical manifestation or slowing progression in patients with acute, early-chronic, and re-activated disease. They have limited efficacy, however, in achieving parasitological cure.

Preferred Therapy for Acute, Early Chronic, and Re-Activated Disease

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days (**BIII**) (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Alternative Therapy

- Nifurtimox 8–10 mg/kg/day PO for 90–120 days (**CIII**) (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Note:

- Optimal duration of therapy has not been studied in HIV-infected patients.
- Initiation or optimization of ART in patients undergoing treatment for Chagas disease, once the patient is clinically stable (**AIII**)
- Even with treatment, mortality is high in patients with symptomatic reactivation.

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; PO = orally

References

1. Bittencourt AL. Congenital Chagas disease. *Am J Dis Child*. Jan 1976;130(1):97-103. Available at <http://www.ncbi.nlm.nih.gov/pubmed/813519>.
2. Maguire J. Trypanosomiasis. In: Gorbach S. BJ, Blacklow, N., ed. *Infectious Diseases*: Lippincott, Williams & Wilkins; 2004:2327-2334.
3. Benchimol Barbosa PR. The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks. *Int J Cardiol*. Sep 10 2006;112(1):132-133. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16600406>.
4. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. Apr 17 2010;375(9723):1388-1402. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20399979>.
5. Organizacion Panamericana de la Salud. Estimacion cuantativa de la enfermedad de Chagas en las Americas.

Montevideo, Uruguay, Organizacion Panamericana de la Salud. 2006.

6. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop.* Jul-Aug 2010;115(1-2):22-27. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19646412>.
7. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz.* Jul 2003;98(5):577-591. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12973523>.
8. Dorn PL, Perniciaro L, Yabsley MJ, et al. Autochthonous transmission of *Trypanosoma cruzi*, Louisiana. *Emerg Infect Dis.* Apr 2007;13(4):605-607. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17553277>.
9. Herwaldt BL, Grijalva MJ, Newsome AL, et al. Use of polymerase chain reaction to diagnose the fifth reported US case of autochthonous transmission of *Trypanosoma cruzi*, in Tennessee, 1998. *J Infect Dis.* Jan 2000;181(1):395-399. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10608796>.
10. Kjos SA, Snowden KF, Craig TM, Lewis B, Ronald N, Olson JK. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol.* Apr 15 2008;152(3-4):249-256. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18255233>.
11. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet.* Jun 8 1985;1(8441):1332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2860516>.
12. Centers for Disease C, Prevention. Blood donor screening for chagas disease—United States, 2006-2007. *MMWR Morb Mortal Wkly Rep.* Feb 23 2007;56(7):141-143. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17318113>.
13. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. *Curr Opin Infect Dis.* Oct 2008;21(5):476-482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18725796>.
14. Bern C, Verastegui M, Gilman RH, et al. Congenital *Trypanosoma cruzi* transmission in Santa Cruz, Bolivia. *Clin Infect Dis.* Dec 1 2009;49(11):1667-1674. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19877966>.
15. Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg.* Mar 1994;50(3):261-268. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8147485>.
16. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol.* Jan 2007;101(1):31-50. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17244408>.
17. Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid biology and disease.* May 13 2004;3(1):2. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15142278>.
18. Committee WHOE. Control of Chagas disease. *World Health Organ Tech Rep Ser.* 2002;905:i-vi, 1-109, back cover. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12092045>.
19. Rassi A, Jr., Rassi A, Little WC. Chagas' heart disease. *Clin Cardiol.* Dec 2000;23(12):883-889. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11129673>.
20. Rassi A, Jr., Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol.* Jan 2001;76(1):75-96. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11175486>.
21. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroenterol.* Jun 1998;93(6):884-889. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9647012>.
22. Campos SV, Strabelli TM, Amato Neto V, et al. Risk factors for Chagas' disease reactivation after heart transplantation. *J Heart Lung Transplant.* Jun 2008;27(6):597-602. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18503957>.
23. Kohl S, Pickering LK, Frankel LS, Yaeger RG. Reactivation of Chagas' disease during therapy of acute lymphocytic leukemia. *Cancer.* Sep 1 1982;50(5):827-828. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6807527>.
24. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis.* Sep 1999;29(3):561-567. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10530448>.
25. Sartori AM, Neto JE, Nunes EV, et al. *Trypanosoma cruzi* parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. *J Infect Dis.* Sep 15 2002;186(6):872-875. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12198628>.
26. Sartori AM, Lopes MH, Benvenuti LA, et al. Reactivation of Chagas' disease in a human immunodeficiency virus-

- infected patient leading to severe heart disease with a late positive direct microscopic examination of the blood. *Am J Trop Med Hyg.* Nov 1998;59(5):784-786. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9840598>.
27. Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992-2007. *Int J Infect Dis.* Nov 2008;12(6):587-592. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18337139>.
 28. Diazgranados CA, Saavedra-Trujillo CH, Mantilla M, Valderrama SL, Alquichire C, Franco-Paredes C. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet Infect Dis.* May 2009;9(5):324-330. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19393962>.
 29. Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, Rocha A. Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. *Clin Infect Dis.* Dec 1997;25(6):1397-1400. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9431385>.
 30. Leiby DA, Wendel S, Takaoka DT, Fachini RM, Oliveira LC, Tibbals MA. Serologic testing for *Trypanosoma cruzi*: comparison of radioimmunoprecipitation assay with commercially available indirect immunofluorescence assay, indirect hemagglutination assay, and enzyme-linked immunosorbent assay kits. *J Clin Microbiol.* Feb 2000;38(2):639-642. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10655360>.
 31. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gurtler RE. The challenges of Chagas Disease—grim outlook or glimmer of hope. *PLoS Med.* Dec 2007;4(12):e332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18162039>.
 32. Sosa-Estani S, Gamboa-Leon MR, Del Cid-Lemus J, et al. Use of a rapid test on umbilical cord blood to screen for *Trypanosoma cruzi* infection in pregnant women in Argentina, Bolivia, Honduras, and Mexico. *Am J Trop Med Hyg.* Nov 2008;79(5):755-759. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18981518>.
 33. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic *Trypanosoma cruzi* infection. *Am J Trop Med Hyg.* Mar 2009;80(3):410-415. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19270291>.
 34. Gorlin J, Rossmann S, Robertson G, et al. Evaluation of a new *Trypanosoma cruzi* antibody assay for blood donor screening. *Transfusion.* Mar 2008;48(3):531-540. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18067497>.
 35. Junqueira AC, Chiari E, Wincker P. Comparison of the polymerase chain reaction with two classical parasitological methods for the diagnosis of Chagas disease in an endemic region of north-eastern Brazil. *Trans R Soc Trop Med Hyg.* Mar-Apr 1996;90(2):129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8761570>.
 36. Wincker P, Telleria J, Bosseno MF, et al. PCR-based diagnosis for Chagas' disease in Bolivian children living in an active transmission area: comparison with conventional serological and parasitological diagnosis. *Parasitology.* Apr 1997;114 (Pt 4):367-373. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9107023>.
 37. Feilij H, Muller L, Gonzalez Cappa SM. Direct micromethod for diagnosis of acute and congenital Chagas' disease. *J Clin Microbiol.* Aug 1983;18(2):327-330. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6413530>.
 38. Duffy T, Bisio M, Altcheh J, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. *PLoS Negl Trop Dis.* 2009;3(4):e419. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19381287>.
 39. Schijman AG, Vigliano C, Burgos J, et al. Early diagnosis of recurrence of *Trypanosoma cruzi* infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. *J Heart Lung Transplant.* Nov 2000;19(11):1114-1117. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11077230>.
 40. Mott KE, Muniz TM, Lehman JS, Jr., et al. House construction, triatomine distribution, and household distribution of seroreactivity to *Trypanosoma cruzi* in a rural community in northeast Brazil. *Am J Trop Med Hyg.* Nov 1978;27(6):1116-1122. Available at <http://www.ncbi.nlm.nih.gov/pubmed/103445>.
 41. Kroeger A, Villegas E, Ordóñez-González J, Pabon E, Scorza JV. Prevention of the transmission of Chagas' disease with pyrethroid-impregnated materials. *Am J Trop Med Hyg.* Mar 2003;68(3):307-311. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12685636>.
 42. Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. *Clin Microbiol Rev.* Jan 2005;18(1):12-29. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15653816>.
 43. Rodrigues Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz.* Jan 2002;97(1):3-24. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11992141>.
 44. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic

- review. *JAMA*. Nov 14 2007;298(18):2171-2181. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18000201>.
45. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). *Human & experimental toxicology*. Aug 2006;25(8):471-479. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16937919>.
 46. Pinazo MJ, Espinosa G, Gallego M, Lopez-Chejade PL, Urbina JA, Gascon J. Successful treatment with posaconazole of a patient with chronic Chagas disease and systemic lupus erythematosus. *Am J Trop Med Hyg*. Apr 2010;82(4):583-587. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20348503>.
 47. Torrico F, Alonso-Vega C, Suarez E, et al. Maternal Trypanosoma cruzi infection, pregnancy outcome, morbidity, and mortality of congenitally infected and non-infected newborns in Bolivia. *Am J Trop Med Hyg*. Feb 2004;70(2):201-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14993634>.
 48. Di Pentima MC, Hwang LY, Skeeter CM, Edwards MS. Prevalence of antibody to Trypanosoma cruzi in pregnant Hispanic women in Houston. *Clin Infect Dis*. Jun 1999;28(6):1281-1285. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10451166>.
 49. Bittencourt AL. Possible risk factors for vertical transmission of Chagas' disease. *Revista do Instituto de Medicina Tropical de Sao Paulo*. Sep-Oct 1992;34(5):403-408. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1342103>.
 50. Scapellato PG, Bottaro EG, Rodriguez-Brieschke MT. Mother-child transmission of Chagas disease: could coinfection with human immunodeficiency virus increase the risk? *Rev Soc Bras Med Trop*. Mar-Apr 2009;42(2):107-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19448923>.
 51. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis*. Sep 1995;21(3):551-555. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8527542>.
 52. Freilij H, Altcheh J, Muchinik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J*. Feb 1995;14(2):161-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7746707>.
 53. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Assessment of cytogenetic damage in chagasic children treated with benznidazole. *Mutation research*. Oct 1988;206(2):217-220. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3140001>.
 54. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutation research*. Oct 1989;224(2):263-267. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2507913>.
 55. de Toranzo EG, Masana M, Castro JA. Administration of benznidazole, a chemotherapeutic agent against Chagas disease, to pregnant rats. Covalent binding of reactive metabolites to fetal and maternal proteins. *Archives internationales de pharmacodynamie et de therapie*. Nov 1984;272(1):17-23. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6440493>.
 56. Oliveira I, Torrico F, Munoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. Aug 2010;8(8):945-956. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20695749>.

Isosporiasis (Cystoisosporiasis) (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.¹⁻⁷ Although *Isospora* (*Cystoisospora*) *belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.² Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.⁶⁻¹² Acalculous cholecystitis/cholangiopathy^{2,13-15} and reactive arthritis¹⁶ also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36 μm by 12–17 μm) in fecal specimens.² Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they autofluoresce.^{2,17} Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.^{2,10} Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.^{2,18-20}

Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.^{1,3,4,21} In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).¹ In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm³.³ After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in patients with versus without a history of *Pneumocystis pneumonia*—indirect evidence of a protective effect from use of TMP-SMX for *Pneumocystis pneumonia*.⁴ Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas.

Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients (**AIII**). TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis (**AI**). It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails (**AIII**).

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.^{6,7,22} The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of the initial studies,^{6,7} the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily (**AII**).²³ In another study, TMP-SMX (160/800 mg) administered twice daily was also effective (**BI**).²² Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)^{6,10} if symptoms worsen or persist (**BIII**). Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.^{2,9,10,24–26} However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States (**CIII**); it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,²⁷ and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.^{3,28,29} Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients (**BIII**).

Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.^{3,14,21} Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption (**AIII**).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent (**CI**). On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.²²

Unsubstantiated or mixed data are available for albendazole,^{29–31} nitazoxanide,^{32,33} doxycycline,³⁴ the macrolides roxithromycin and spiramycin,^{25,35,36} and the veterinary anticoccidial agent diclazuril (**CIII**).^{37,38}

Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.^{8,25,26,28,35,37} Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm³ should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections (**AI**). In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.^{6,7,22} In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) (**AI**).⁷ Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective (**BIII**);^{5,10} however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.¹⁴

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used (**BIII**).²⁸ On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative (**CI**).²²

When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm³ for >6 months after initiation of ART (**BIII**).

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,³⁹⁻⁴² TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection (**CIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.⁴³ Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.⁴⁴

Recommendations for Treating *Isospora belli* Infection

Treating *Isospora belli* Infection

General Management Considerations:

- Fluid and electrolyte support in patients with dehydration (**AIII**)
- Nutritional supplementation for malnourished patients (**AIII**)

Preferred Therapy for Acute Infection:

- TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days (**AII**), or
- TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days (**BI**)
- One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (**BIII**)
- IV therapy for patients with potential or documented malabsorption

Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):

- Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily (**BIII**), or
- Ciprofloxacin 500 mg PO BID for 7 days (**CI**)

Chronic Maintenance Therapy (Secondary Prophylaxis)

(In Patients with CD4 Count $<200/\text{mm}^3$)

Preferred Therapy:

- TMP-SMX (160 mg/800 mg) PO 3 times weekly (**AI**)

Alternative Therapy:

- TMP-SMX (160 mg/800 mg) PO daily (**BIII**), or
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly (**BIII**), or
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (**BIII**)
- Ciprofloxacin 500 mg PO 3 times weekly (**CI**) as a second line alternative

Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count >200 cells/ mm^3 for >6 months in response to ART and without evidence of active *I. belli* infection (**BIII**)

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. 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>.
2. 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>.
3. Guiguet M, Furco A, Tattevin P, Costagliola D, Molina JM, French Hospital Database on HIVCEG. HIV-associated *Isospora belli* infection: incidence and risk factors in the French Hospital Database on HIV. *HIV Med*. Mar 2007;8(2):124-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17352769>.
4. Sorvillo FJ, Lieb LE, Seidel J, Kerndt P, Turner J, Ash LR. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. *Am J Trop Med Hyg*. Dec 1995;53(6):656-659. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8561272>.
5. Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. *Am J Trop Med Hyg*. Aug 2003;69(2):217-222. Available at <http://www.ncbi.nlm.nih.gov/pubmed/13677379>.
6. DeHovitz JA, Pape JW, Boney M, Johnson WD, Jr. Clinical manifestations and therapy of *Isospora belli* infection in *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* T-37

- 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>.
7. 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>.
 8. Forthal DN, Guest SS. *Isospora belli* enteritis in three homosexual men. *Am J Trop Med Hyg*. Nov 1984;33(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6507724>.
 9. Modigliani R, Bories C, Le Charpentier Y, et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. *Gut*. Feb 1985;26(2):179-187. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4038492>.
 10. Whiteside ME, Barkin JS, May RG, Weiss SD, Fischl MA, MacLeod CL. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. Nov 1984;33(6):1065-1072. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6334448>.
 11. 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>.
 12. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated *Isospora belli* diarrhea. *J Emerg Med*. Dec 2011;41(6):e129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18993015>.
 13. Benator DA, French AL, Beaudet LM, Levy CS, Orenstein JM. *Isospora belli* infection associated with acalculous cholecystitis in a patient with AIDS. *Ann Intern Med*. Nov 1 1994;121(9):663-664. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7944075>.
 14. Lagrange-Xelot M, Porcher R, Sarfati C, et al. Isosporiasis in patients with HIV infection in the highly active antiretroviral therapy era in France. *HIV Med*. Feb 2008;9(2):126-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18257775>.
 15. Walther Z, Topazian MD. *Isospora* cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. Sep 2009;40(9):1342-1346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447468>.
 16. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM, Jurado R, Torre-Cisneros J. *Isospora belli* reactive arthritis in a patient with AIDS. *Annals of the rheumatic diseases*. Sep 1994;53(9):618-619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7979603>.
 17. Bialek R, Binder N, Dietz K, Knobloch J, Zelck UE. Comparison of autofluorescence and iodine staining for detection of *Isospora belli* in feces. *Am J Trop Med Hyg*. Sep 2002;67(3):304-305. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12408672>.
 18. Frenkel JK, Silva MB, Saldanha J, et al. *Isospora belli* infection: observation of unicellular cysts in mesenteric lymphoid tissues of a Brazilian patient with AIDS and animal inoculation. *The Journal of eukaryotic microbiology*. 2003;50 Suppl:682-684. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14736218>.
 19. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. *Am J Clin Pathol*. Apr 1987;87(4):536-542. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3826017>.
 20. Bernard E, Delgiudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 1997;16(9):699-701. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9352268>.
 21. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. Jun 2009;80(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19478276>.
 22. 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>.
 23. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. Feb 1 2001;32(3):331-351. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11170940>.
 24. Mojon M, Coudert J, E.O. dL. Serious isosporosis by *Isospora belli*: a case report treated by Fansidar [Abstract]. *Southeast Asian J Trop Med Public Health*. 12:449-500. 1981.

25. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by *Isospora belli*: therapeutic response to pyrimethamine and sulfadiazine. *Diagn Microbiol Infect Dis*. Oct 1996;26(2):87-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8985661>.
26. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. May 1974;66(5):923-935. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4826994>.
27. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2860516>.
28. 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>.
29. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scandinavian journal of infectious diseases*. 2002;34(11):859-862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12578164>.
30. 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>.
31. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Alimentary pharmacology & therapeutics*. 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.
32. 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>.
33. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. Jun 1997;56(6):637-639. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9230795>.
34. Meyohas MC, Capella F, Poirot JL, et al. [Treatment with doxycycline and nifuroxazide of *Isospora belli* infection in AIDS]. *Pathologie-biologie*. Jun 1990;38(5 (Pt 2)):589-591. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2385457>.
35. 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>.
36. 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>.
37. Limson-Pobre RN, Merrick S, Gruen D, Soave R. Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis*. Jan 1995;20(1):201-202. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7727660>.
38. Kayembe K, Desmet P, Henry MC, Stoffels P. Diclazuril for *Isospora belli* infection in AIDS. *Lancet*. Jun 17 1989;1(8651):1397-1398. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2567420>.
39. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11738517>.
40. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11096168>.
41. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *American journal of epidemiology*. May 15 2001;153(10):961-968. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11384952>.
42. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sexually transmitted infections*. Dec 2001;77(6):441-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11714944>.
43. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. Jul-Aug 2001;95(4):424-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11579889>.
44. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. May 2006;107(5):1120-1138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16648419>.