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

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Malaria (Last updated May 7, 2013; last reviewed May 7, 2013)

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. 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. 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.

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). Although P. vivax infections are more common and occur in a far wider geographic distribution, 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. Malaria influences the natural history of HIV infection, and HIV infection alters the natural history and severity of malaria.

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. Failure to take appropriate chemoprophylaxis is a common problem for both groups of individuals. People who formerly lived in malarious areas may believe that they are immune, and therefore, do not need to take prophylaxis. 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. Malaria is a surprisingly common cause of these fevers.

Clinical Manifestations
The clinical syndromes caused by Plasmodium species depend on prior exposure. 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.

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. 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.

**Effects of Malaria on Mother-to-Child HIV Transmission**

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages and increased viral load, 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, but studies from Kenya did not demonstrate this association.

**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.

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 12–24-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-
Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis. 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. 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.

**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. 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.

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. CDC posts current treatment recommendations on its website 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. 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, 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:

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*Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* T-8
Penicilliosis marneffei  (Last updated May 7, 2013; last reviewed May 7, 2013)

**Epidemiology**

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, 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.¹⁻³ 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. marneffei* 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. marneffei*.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.\textsuperscript{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/mm\(^3\) 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 (B\textsuperscript{I}). The preferred drug for prophylaxis is oral itraconazole, 200 mg/day (B\textsuperscript{I}). An alternative drug is oral fluconazole 400 mg once weekly (B\textsuperscript{II}). Primary prophylaxis is not indicated in other geographic areas.\textsuperscript{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/mm\(^3\).\textsuperscript{16} Therefore, primary prophylaxis for penicilliosis can logically be discontinued in AIDS patients who receive combination ART and have CD4 counts >100 cells/mm\(^3\) for ≥6 months but there are no convincing data addressing this issue (C\textsuperscript{II}). Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm\(^3\) (B\textsuperscript{III}).

**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 (A\textsuperscript{II}), followed by secondary prophylaxis.\textsuperscript{17} Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (B\textsuperscript{II}),\textsuperscript{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 (B\textsuperscript{II}).\textsuperscript{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/mm\(^3\), ART should be started as soon as possible after the initiation of antifungal therapy (B\textsuperscript{III}). In patients with CD4 counts >50 cells/mm\(^3\), it may be prudent to delay initiation of ART until after completion of the first 2 weeks of induction therapy for penicilliosis (C\textsuperscript{III}).

**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 (B\textsuperscript{II}). 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 (A\textsuperscript{III}). The serum concentration should be >1 µg/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. 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 marneffei* 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


Leishmaniasis  (Last updated May 9, 2014; last reviewed May 7, 2013)

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/µL (56%–95%); and thrombocytopenia usually is present.
Splenomegaly is less pronounced in HIV-co-infected patients than in immunocompetent patients with visceral leishmaniasis. 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. Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis. Non-ulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described. 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.

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.

**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.

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). Serologic tests to detect antibodies against Leishmania antigens have high sensitivity to diagnose visceral leishmaniasis in immunocompetent patients. 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. The use of recombinant antigen in ELISA assays may increase sensitivity, but a proportion of co-infected patients remain seronegative. Immunoblotting with Leishmania infantum soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of European patients. 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). Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV co-infection.

**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. Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than conventional amphotericin B (amphotericin B deoxycholate) or pentavalent antimony (sodium stibogluconate). 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). The optimal amphotericin B dosage has not been determined. 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). 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%. 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. 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). 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. 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. 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 (BII), as previously outlined, or pentavalent antimony (sodium stibogluconate), depending on the form of the disease and the clinical response (BIII). 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. 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). 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/µL (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. 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. 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 (CII). 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). 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. 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. 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. 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. 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. Retropective 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. 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). The alternatives are amphotericin B deoxycholate (AIII) or pentavalent antimony (sodium stibogluconate) (AIII). Miltefosine is teratogenic and is contraindicated in pregnancy. Perinatal transmission of *Leishmania spp.* is rare; 13 documented cases have been reported. No data are available on the risk of transmission of *Leishmania spp.* in HIV-infected pregnant women.
### 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 (BII), 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, intralosomal 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

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


Chagas Disease  (Last updated May 7, 2013; last reviewed May 7, 2013)

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 Romaña’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.4,5 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.\textsuperscript{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.\textsuperscript{25} Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts <200 cells/mm\textsuperscript{3}, a history of prior opportunistic infections, or both.\textsuperscript{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).\textsuperscript{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.\textsuperscript{16,17} Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation or rapid progression of existing chronic cardiomyopathy.\textsuperscript{16,29} Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach or intestine.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32,33} Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{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. 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. 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. 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. 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. 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. 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. 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. 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.

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. 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. Limited data suggest that early recognition and treatment of reactivation may improve prognosis.

Neither anti-trypanosomal drug is licensed in the United States; however, the drugs are available from the
**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.\textsuperscript{47} Limited data suggest that the rate of congenital transmission is higher for HIV-infected women than in immunocompetent mothers.\textsuperscript{16,50} Infants co-infected with HIV and \textit{T. cruzi} also may be more likely to have symptoms, especially neurologic symptoms.\textsuperscript{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.\textsuperscript{53,54} Benznidazole crosses the placenta in rats and covalently binds to fetal proteins.\textsuperscript{55} Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute \textit{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 \textit{T. cruzi} infection, ART should be initiated (AIII). All infants born to \textit{T. cruzi}-infected women should undergo appropriate testing for congenitally acquired \textit{T. cruzi} infection and be treated promptly if infection is confirmed.\textsuperscript{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 \textit{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 (AII)
- 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


26. Sartori AM, Lopes MH, Benvenuti LA, et al. Reactivation of Chagas' disease in a human immunodeficiency virus-


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 arthritis\(^16\) 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/mm\(^3\).\(^3\) 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.

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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. 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, the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily (AII). In another study, TMP-SMX (160/800 mg) administered twice daily was also effective (BII). 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) 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. 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, 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. 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. 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 (C). 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.

Unsubstantiated or mixed data are available for albendazole, nitazoxanide, doxycycline, the macrolides roxithromycin and spiramycin, and the veterinary anticoccidial agent diclazuril (CIII).
Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.\textsuperscript{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/mm\(^3\) should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against \textit{Pneumocystis jirovecii} and \textit{Toxoplasma gondii} infections (\textbf{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.\textsuperscript{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) (\textbf{AI}).\textsuperscript{7} Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective (\textbf{BIII});\textsuperscript{5,10} however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.\textsuperscript{14}

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used (\textbf{BIII}).\textsuperscript{28} On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative (\textbf{CI}).\textsuperscript{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 \textit{I. belli} infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm\(^3\) for >6 months after initiation of ART (\textbf{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,\textsuperscript{39–42} TMP-SMX therapy should be provided in the setting of maternal symptomatic \textit{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 (\textbf{CIII}). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.\textsuperscript{43} Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.\textsuperscript{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 Sulfonamide 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/mm³)

**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/mm³ 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**


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