



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

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Epidemiology

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

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

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

Clinical Manifestations

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

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

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

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

Diagnosis

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

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

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

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

Preventing Exposure

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

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

Preventing Disease

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

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

Treating Disease

Visceral Leishmaniasis

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

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

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

Cutaneous Leishmaniasis

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

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

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

Special Considerations with Regard to Starting ART

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

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

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

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

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

Managing Treatment Failure

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

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

Preventing Recurrence

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

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

When to Stop Secondary Prophylaxis

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

Special Considerations During Pregnancy

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

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

Preferred Therapy:

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

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 **(All)**

Preferred Therapy:

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

Alternative Therapy:

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

Discontinuation of Chronic Maintenance Therapy

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

Treating Cutaneous Leishmaniasis

Preferred Therapy:

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

Alternative Therapy:

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

Chronic Maintenance Therapy for Cutaneous Leishmaniasis

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

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

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