Leishmaniasis

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Epidemiology

Leishmaniasis is caused by protozoa that survive and replicate within macrophages and other mononuclear cells. There are over 20 species within the *Leishmania* (*L.*) genus that cause human disease, the main forms of which are visceral, cutaneous, and mucosal disease.[1] Leishmaniasis occurs in 99 countries or territories in the tropics and subtropics (including the southern United States, most of Central and South America, and southern Europe), with an estimated incidence of 1 million new cases annually. In 2022, 12,842 incident cases of visceral leishmaniasis and 205,986 new cases of cutaneous leishmaniasis were reported to the World Health Organization (WHO).[2]

Prevalence of the different *Leishmania* species varies geographically. The main *Leishmania* species that cause visceral leishmaniasis are *L. donovani, L. infantum* (syn. *L. chagasi*), and the more recently recognized *L. (Mundinia) martiniquensis*. The visceral leishmaniasis-causing species in the Americas are *L. infantum* and *L. martiniquensis*. Cutaneous leishmaniasis acquired outside the Americas is commonly caused by *L. tropica, L. major,* and *L. aethiopica*. In the Americas, the prevalent species that cause cutaneous leishmaniasis are of the *L.* (*Viannia)* subgenera (*braziliensis, guyanensis, panamensis, peruviana), L. mexicana* and *L. amazonensis*.[3] In the United States, there have been fewer than 100 recognized autochthonous cases in the past 100 years, mainly *L. mexicana* cutaneous leishmaniasis acquired in Texas.[3]

As of 2021, HIV-leishmaniasis coinfection has been reported in 45 countries,[4] predominantly as HIV-visceral leishmaniasis coinfection.[4,5] The first cases of HIV-leishmaniasis coinfection were described in Spain in the late 1980s.[6] After the introduction of combination antiretroviral therapy (ART), the incidence decreased substantially in developed countries,[7,8] but HIV-leishmaniasis coinfection poses a growing problem in parts of Asia, Africa, and Latin America.[9-12] New species *Leishmania (Mundinia) martiniquensis,* associated with visceral and disseminated cutaneous leishmaniasis, and *L. (Mundinia) orientalis*, which causes cutaneous leishmaniasis, have been reported from Thailand in people with HIV.[11-13]

In endemic areas, leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*. However, in southern Europe, HIV and *L. infantum* visceral leishmaniasis coinfections have been reported in association with injection drug use, suggesting that *Leishmania* (which can infrequently be transmitted via blood[14,15]) also may be acquired by needle sharing; contaminated syringes have been shown to be an epidemiologically significant component of the transmission cycle of *Leishmania* amastigotes.[16,17]

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous leishmaniasis 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.[18] The most reported clinical presentation of leishmaniasis in people with HIV is a systemic visceral disease syndrome. However, the predominant

parasite species varies geographically. In Europe, visceral disease has been reported in 95% of people with HIV-leishmaniasis coinfection (87% typical visceral, 8% atypical visceral).[6] In Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported leishmaniasis cases in people with HIV, respectively.[19]

Most *Leishmania* 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.[20-22] After primary infection, *Leishmania* remain viable in healthy individuals for long periods, creating a population at risk of reactivation if CD4 T lymphocyte (CD4) cell depletion occurs. In people with HIV without severe CD4 cell depletion, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 count <200 cells/mm^3), manifestations of leishmaniasis can be both atypical and more severe. Dermotrophic species can disseminate both in skin and through the reticuloendothelial system to visceralize.[23,24] Relapse after treatment—especially of visceral leishmaniasis—is common.[25,26] Atypical disseminated leishmaniasis in people with HIV is considered a WHO clinical stage 4 HIV criterion.[27]

Visceral Leishmaniasis

In people with HIV and visceral disease, the most common clinical and laboratory findings are fever (65% to 100%), systemic malaise (70% to 90%), splenomegaly (usually moderate) (54% to 90%), hepatomegaly without splenomegaly (34% to 85%), hepatosplenomegaly (68% to 73%), lymphadenopathy (12% to 57%), and pancytopenia (50% to 80%).[6,26] Anemia is usually marked, with <10 g hemoglobin/dL (50% to 100%); leukopenia is moderate, with <2,400 leukocytes/μL (56% to 95%); and thrombocytopenia is usually present (52% to 93%). Splenomegaly is less pronounced in people with HIV than in immunocompetent patients with visceral leishmaniasis.[26] In people with HIV with more profound CD4 cell depletion, atypical manifestations have been described, including mucosal involvement, such as masses, ulcers, mucositis of the upper and lower gastrointestinal tract, serositis in pleural and peritoneal cavities, and lung and skin lesions.[6,7,26,28,29] Esophageal involvement can lead to dysphagia and odynophagia and must be distinguished from other causes of esophagitis in people with HIV, such as candidiasis.[6] Amastigote infiltration of the duodenum often presents as chronic diarrhea.[7] Nonulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described in people with HIV and visceral leishmaniasis.[30-32] 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.[33,34]

Cutaneous Leishmaniasis

Cutaneous leishmaniasis in people with HIV varies depending on immune function. In people with HIV with well-controlled HIV and high CD4 counts, the presentation is not different than those without HIV except that there may be a higher rate of relapse.[35,36] In those with lower CD4 counts (e.g., <200 cells/mm^3), dermal leishmaniasis may disseminate in the skin, mucosa, and viscera.[37] Most have multiple skin lesions, often atypical (unusual morphology) for localized cutaneous leishmaniasis, and genital involvement seems more frequent.[37-39] Among people with HIV in Brazil, 68% had concomitant mucosal leishmaniasis, a rate much higher than those without HIV.[18] Additionally, as mentioned above, people with HIV and visceral leishmaniasis may present with cutaneous lesions.[40,41]

Mucosal Leishmaniasis

Mucosal leishmaniasis among people with HIV is most commonly associated with infections acquired in the New World, especially *L. braziliensis* and other species in the *L. (Viannia)* subgenera including *L. guyanensis* and *L. panamensis*.[19] Additionally, mucosal disease also has been reported with species that have geographic distribution beyond the Americas, including *L. infantum*, *L. aethiopica*, and *L. tropica*.[42] Presentation in people with HIV is similar to those without HIV and includes nasal septum destruction, obstructive masses in the nose, uvula erosion, ulcerated infiltrative lesions of the palate, and laryngeal involvement.[19,43-49] Mucosal leishmaniasis may occur concomitantly with cutaneous leishmaniasis or years after resolution of localized cutaneous leishmaniasis.[50]

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, smears, and molecular methods in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in people with HIV. Coinfection of HIV and visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in the following: blood smears (approximately 50% sensitivity in expert hands); buffy-coat smear preparations; cultures from the peripheral blood; and smears, histopathology, and cultures from bone marrow (preferred) or splenic aspirates (significant procedural risk). Polymerase chain reaction (PCR) amplification can also be useful for detecting *Leishmania* nucleic acid in the blood or tissue of patients with HIV-leishmaniasis coinfection (>95% sensitivity).[51] Generally, PCR and *Leishmania* culture require specialty reference laboratory support. Assistance for conducting diagnostic tests for *Leishmania* is available by contacting the Centers for Disease Control and Prevention (CDC) at parasiteslab@cdc.gov.

Serologic tests that detect *Leishmania* antibodies have high sensitivity and can be used to support diagnosis of visceral leishmaniasis in immunocompetent patients.[51] They should be used only in those with a compatible clinical picture and an exposure history suggestive of visceral leishmaniasis. Serology has a lower sensitivity in people with HIV such that parasitological diagnosis should be sought when clinical suspicion has been raised.[6,52] The use of recombinant antigen in enzyme-linked immunosorbent assays (or ELISAs) may increase sensitivity for detection of *Leishmania* antibodies, but a proportion of people with HIV-leishmaniasis coinfection remain seronegative.[53] Immunoblotting with *L. infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of patients.[52]

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in urban and periurban areas with zoonotic transmission (such as controlling visceral leishmaniasis in dogs) and vector control activities (such as indoor residual spraying, using insecticide-treated bed nets, and intervening in sand fly breeding sites).[54,55] Optimal control measures rely on local transmission characteristics, which vary by vector. For travelers to leishmaniasis-endemic areas, the best way 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.

People who inject drugs should undertake measures (such as the use of clean needles and injection equipment from syringe service programs) to decrease the risk of transmission of *Leishmania* parasites and other infectious agents.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended. No screening or preemptive therapy is appropriate for people with HIV who may have been exposed to leishmanial infection. No vaccine against leishmaniasis is available.

Treating Disease

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

- ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of visceral leishmaniasis.

Leishmania infantum/chagasi

Preferred Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)

Alternative Therapy

- Amphotericin B deoxycholate* 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BII), currently available in the United States only by investigator-initiated investigational new drug application

Leishmania donovani

Preferred Therapy (Combination)

- Liposomal amphotericin B* 30 mg/kg IV total dose (5 mg/kg on Days 1, 3, 5, 7, 9, and 11), plus miltefosine 50 mg PO twice daily for 28 days (East Africa) or for 14 days (Southeast Asia) (BI)

Alternative Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)
- See Alternative Therapy for *L. infantum*, *or*
- For Indian *L. donovani*
  - Miltefosine (BII) (available in the United States via www.profounda.com), aiming for 2.5–3 mg/kg daily (maximum of 150 mg daily)
    - For patients who weigh 30–44 kg: 50 mg PO two times daily for 28 days
    - For patients who weigh ≥45 kg: 50 mg PO three times daily for 28 days

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm^3 (AII)

Preferred Therapy

- Liposomal amphotericin B* 4 mg/kg IV every 2–4 weeks (AII)

Alternative Therapy

- Amphotericin B lipid complex* 3 mg/kg every 21 days (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM every 4 weeks (BII), *or*
- Pentamidine isethionate 4 mg/kg (maximum of 300 mg) IV every 2–4 weeks (BII)

Discontinuation of Chronic Maintenance Therapy

- Consider stopping secondary prophylaxis when the CD4 count is >350 cells/mm^3, HIV viral load has been undetectable for 6 months, and there are no symptoms of visceral leishmaniasis relapse (CIII).

Treating Cutaneous Leishmaniasis
• ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of cutaneous leishmaniasis. *Preferred Therapy* • Liposomal amphotericin B* 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) until a total dose of 20–60 mg/kg is achieved (BIII), *or* • Miltefosine 2.5 mg/kg/day PO in 2 or 3 divided doses for 28 days (*Viannia* subgenus); not well tolerated if more than 150 mg daily (BIII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BIII) *Alternative Therapy* • Other options for individual cases may include cryotherapy, topical paromomycin, intralesional pentavalent antimony (meglumine antimoniate) or pentamidine, fluconazole for *L. major* and *L. mexicana*, intravenous pentamidine or local heat therapy. Chronic Maintenance Therapy for Cutaneous Leishmaniasis • Indicated for immunocompromised patients with multiple relapses (CIII) • See drugs and doses for *Chronic Maintenance Therapy for Visceral Leishmaniasis*.
Pregnancy Considerations
• Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy (AIII). Amphotericin B deoxycholate can be given as alternative therapy (AIII). • In many uncomplicated cutaneous leishmaniasis cases, treatment can be delayed until postpartum (CIII). • In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, shared decision making with the patient is recommended to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) (CIII). • Liposomal amphotericin B IV is the first choice for therapy of mucosal or severe cutaneous leishmaniasis in pregnancy (CIII).

* Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions (AII). Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine (CIII). An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to help reduce the risk of renal dysfunction during treatment (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IM = intramuscular; IV = intravenous; PO = orally

Visceral Leishmaniasis

The following medications have been used to treat visceral leishmaniasis: amphotericin B deoxycholate, liposomal amphotericin B, pentavalent antimonial drugs (e.g., meglumine antimoniate), and miltefosine (for *L. donovani*). Lower cure rates, higher drug toxicity, more relapses, and higher mortality summarize the treatment outcomes for people with HIV with visceral leishmaniasis. Amphotericin deoxycholate and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.[56-58] Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than amphotericin B deoxycholate or pentavalent antimony (meglumine antimoniate).[59-61] The equivalent efficacy and better toxicity profile have led the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and

Adolescents With HIV (the Panel) to recommend liposomal amphotericin B as the preferred amphotericin formulation for treatment of visceral leishmaniasis in people with HIV **(AII).**[62] The optimal amphotericin B dosage has not been determined.[62,63]

Recommended regimens include liposomal preparations of 3 to 5 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).** An alternative regimen of 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, can be administered **(BII).**[56,57,64-67] Pentavalent antimony (meglumine antimoniate) 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, is an alternative **(BII).** Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis). Due to toxicity concerns with pentavalent antimonial drugs, a pregnancy test (beta-human chorionic gonadotropin [β-hCG]) should be obtained by individuals of childbearing potential prior to start of therapy, and effective contraception during treatment is advised.

Oral miltefosine monotherapy (available in the United States via www.profounda.com) is recommended as an alternative treatment option for Indian *L. donovani* visceral leishmaniasis in people with HIV[63,68] at a dose of approximately 2.5 to 3 mg/kg daily (maximum of 150 mg daily) for 28 days **(BII).**[69-72] Combination therapy using miltefosine and liposomal amphotericin in the treatment of HIV-*L. donovani* visceral leishmaniasis has also shown promise. A randomized clinical trial of liposomal amphotericin 30 mg/kg total dose and miltefosine 100 mg/day for 28 days was compared to liposomal amphotericin 40 mg/kg total dose monotherapy among patients with *L. donovani* visceral leishmaniasis and HIV coinfection in Ethiopia. Parasite clearance persisting to 58 days was found in 88% of the combination treatment group versus 55% in the monotherapy group.[73] In India, 150 people with HIV with *L. donovani* visceral leishmaniasis received total doses of liposomal amphotericin 40 mg/kg IV versus liposomal amphotericin 30 mg/kg IV with oral miltefosine 50 mg twice daily for 14 days. At Day 210 follow-up, 7% of patients in the monotherapy arm died versus 1.3% in the combination arm.[74] These data have led the WHO to update their 2022 HIV and visceral leishmaniasis coinfection treatment guidelines to conditionally recommend combination liposomal amphotericin and miltefosine treatment; those with HIV-visceral leishmaniasis coinfection in Eastern Africa (*L. donovani*) should be administered miltefosine for 28 days, and those with HIV-visceral leishmaniasis coinfection (*L. donovani*) in South East Asia should be administered miltefosine for 14 days.[75] Since miltefosine is teratogenic and is contraindicated in pregnancy, β-hCG should be checked prior to initiation and effective contraception should be continued for 5 months.[63]

Data supporting the use of miltefosine monotherapy in people with HIV are relatively limited and restricted to Indian *L. donovani*. For visceral leishmaniasis caused by *L. infantum* (e.g., in the Americas, Europe), Pan American Health Organization guidelines recommend against miltefosine monotherapy due to lower efficacy and limited evidence.[76] Further research is also needed to confirm the efficacy of drug combinations in people with HIV to treat other *Leishmania* species and severe or refractory cases of visceral leishmaniasis in other geographic regions. Currently, there is no recommendation for combination therapy in visceral leishmaniasis due to *L. infantum*.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous leishmaniasis, mucosal leishmaniasis, or diffuse cutaneous leishmaniasis in people with HIV. Based on data from individuals

without HIV with cutaneous leishmaniasis and case reports in people with HIV-cutaneous leishmaniasis, patients with HIV-cutaneous leishmaniasis should be treated with some form of systemic therapy, depending on the type of cutaneous leishmaniasis and the clinical response. Liposomal amphotericin B **(BIII),**[67] miltefosine (*Viannia* subgenus infections) **(BIII),** or pentavalent antimony (meglumine antimoniate) **(BIII)** are options for treatment.[77,78] Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis).

Potential alternatives for cutaneous leishmaniasis include cryotherapy, topical paromomycin, intralesional pentavalent antimony or pentamidine isoethionate, intravenous pentamidine isethionate,[79,80] fluconazole for *L. major* and *L. mexicana*, or local heat therapy. The effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.[66,81-83] However, these alternatives are based on data from people without HIV, not those with HIV-cutaneous leishmaniasis coinfection. For example, although the Pan American Health Organization 2022 guidelines recommend intralesional pentavalent antimonial treatment as first-line use in immunocompetent patients, this treatment has not been tested in people with HIV and New World cutaneous leishmaniasis; because of this, there are concerns about how effectively it will prevent dissemination like mucosal leishmaniasis in people with HIV, who may be at increased risk.[76,84] Therefore, these alternatives could be considered in individualized circumstances in patients with high CD4 counts and controlled viral load.

Special Considerations Regarding ART Initiation

Appropriate use of ART has substantially improved the survival of patients with coinfection and decreased the likelihood of relapse after antileishmanial therapy.[8,26,85] 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).** Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine **(CIII).** An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to 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.[60]

Adverse events associated with miltefosine use include gastrointestinal symptoms (more commonly nausea or vomiting than diarrhea) that can result in prerenal azotemia, motion sickness-like symptoms, scrotal pain, thrombocytopenia, and hepatotoxicity. To decrease gastrointestinal symptoms, which are usually worse at the beginning of therapy, miltefosine should be administered in divided 50 mg doses during the day and taken with food containing some fat. Weekly assessment of renal and hepatic function and platelet counts is recommended.[67]

Patients receiving parenteral pentavalent antimony (meglumine antimoniate) should be monitored closely for adverse reactions.[77] Overall, at a dose of 20 mg/kg of body weight per day, more than 60% of patients have one or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase, or lipase, and clinical pancreatitis, in some patients. Weekly electrocardiograms are recommended during treatment, with careful monitoring for changes that may indicate early cardiotoxicity, such as prolonged QT intervals and T-wave inversion **(CIII).** Rarely, arrhythmias and sudden death have occurred.[58,66] Severe

adverse reactions to pentavalent antimony, including acute pancreatitis and leukopenia, appear to be more common in patients with coinfection than in those who do not have HIV.[86]

Cases of newly symptomatic visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis have been reported in association with immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.[87-90] Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.[91-95] Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

People with HIV who respond to initial treatment should be clinically monitored for relapse (any recurrence or new consistent skin lesions) for at least 6 months to 1 year after treatment for cutaneous leishmaniasis; those with infection with *L. (Viannia)* subspecies also should be followed for 2 to 5 years for any signs or symptoms of inflammation of the nasal mucosa. People with HIV successfully treated for visceral leishmaniasis should be clinically monitored for symptoms or signs of recurrence such as fever, constitutional symptoms, hepatomegaly, splenomegaly, or cytopenia. Routine follow-up via parasitological testing with repeat biopsies or longitudinally tracking antibody levels is generally not recommended for people with HIV with treated leishmaniasis who do not demonstrate clinical signs or symptoms of recurrence. A positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse in people with HIV-visceral leishmaniasis coinfection.[96]

Managing Treatment Failure

For patients who fail to respond to initial therapy or who 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.[97]

In a pharmacokinetic substudy of antileishmanial drugs for treatment of visceral leishmaniasis in people with HIV, blood concentrations of amphotericin were found to be twofold-lower than those measured in studies among those with visceral leishmaniasis without HIV. Additionally, lower observed miltefosine concentrations were likely due in part to lower weight-based dosing when compared to other studies, emphasizing the need to use a weight-based dosage approximating 2.5 mg/kg/day in adults. However, no relationship between amphotericin and miltefosine concentrations and treatment outcome was observed.[98]

Expert assistance to health care providers for clinical care for leishmaniasis is available at the CDC's Parasitic Diseases Hotline at (404) 718-4745 or parasites@cdc.gov.

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of antileishmanial therapy in people with HIV, and relapse is more frequent in those with lower CD4 count.[99] Reported associations with relapse are prior episode of visceral leishmaniasis, CD4 count <100 cells/mm^3 at time of primary visceral leishmaniasis, and no increase in CD4 count at follow-up.[99] In people with HIV-visceral leishmaniasis coinfection 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).[6,100,101] In

Brazil, a relapse rate of 28.6% of patients with HIV-cutaneous leishmaniasis was reported, regardless of viral load and adherence to ART.[35] Therefore, secondary prophylaxis with an effective antileishmanial drug administered at least every 4 weeks is recommended, particularly for patients with visceral leishmaniasis and CD4 counts <200 cells/mm^3 **(AII).**[6,26,100,102]

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex (3 mg/kg every 21 days) in eight patients with no prophylaxis in nine patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.[102] In retrospective observational studies, monthly pentavalent antimony or lipid formulations of amphotericin every 2 to 4 weeks were also associated with decreased relapse rates.[26,100] With a 2 year follow-up, 74 people with HIV-visceral leishmaniasis coinfection were given monthly intravenous pentamidine isethionate (4 mg/kg with a maximal dose 300 mg) and 71% were relapse-free after 12 months.[103] In 54 persons followed for 390 days stratified for CD4 above and below 200, there was a reported overall relapse-free survival of 50% and 53% if CD4 ≥200 cells/µL.[104]

Liposomal amphotericin B (4 mg/kg every 2–4 weeks) **(AII)** is the preferred regimen for secondary prophylaxis. Amphotericin B lipid complex (3 mg/kg every 21 days) **(BII)** and pentavalent antimony (meglumine antimoniate, 20 mg/kg IV or IM every 4 weeks) are alternatives **(BII).** Although pentamidine isethionate is no longer recommended to treat primary visceral leishmaniasis, a dosage of 4 mg/kg IV (300 mg for adult) every 2 to 4 weeks has been suggested as another alternative for secondary prophylaxis **(BII).**[105-107] Allopurinol, used for maintenance therapy, is less effective than monthly pentavalent antimony and **is not recommended (BII).**[100] 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 investigations suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm^3 in response to ART.[105,108] Others, however, suggest that secondary prophylaxis should be maintained indefinitely. Among 74 patients in Ethiopia with HIV-visceral leishmaniasis coinfection, who received monthly intravenous pentamidine for 12 to 18 months, a 36.9% relapse rate was identified over a 2-year follow-up, mainly among those with a low baseline CD4 count of ≤100 cells/mm^3. All with CD4 count >200 cells/mm^3 at Month 12 were relapse-free.[105] In one study, a positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse.[96] Therefore, the Panel recommends considering cessation of secondary prophylaxis when CD4 count is >350 cell/mm^3 and HIV viral load has been undetectable for 6 months and there is no clinical evidence of visceral leishmaniasis relapse **(CIII).**

Special Considerations During Pregnancy

During pregnancy, diagnostic considerations are the same as for other people with HIV. 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.[109,110] Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Several small published series of pregnant women treated with amphotericin B deoxycholate or liposomal amphotericin B have demonstrated good clinical outcomes.[111-115] Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy **(AIII).**[111] Amphotericin B deoxycholate, which has demonstrated positive

clinical and pregnancy outcomes in a small group of pregnant women, can be given as an alternative therapy **(AIII).**[111]

There are concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy; labels for pentavalent antimony compounds state that these drugs are contraindicated for use in pregnancy, although various antimonial compounds were found to not be teratogenic in chickens, rats, or sheep.[116-118] Therefore, pentavalent antimonial drugs are not recommended in pregnancy **(BIII).** Miltefosine is teratogenic and pentamidine is embryotoxic; therefore, both drugs **are not recommended** in pregnancy **(AII).**[63,119] In a systematic review including 346 pregnant women with visceral leishmaniasis, 176 pregnant women treated with liposomal amphotericin were reported to have 4 (2.3%) maternal deaths, 5 (2.8%) miscarriages, and 2 (1.1%) fetal deaths/stillbirths versus 88 pregnant women receiving pentavalent antimonial drugs, where reported outcomes included 4 (4.5%) maternal deaths, 24 (27.3%) spontaneous abortions, and 2 (2.3%) miscarriages.[115]

In contrast to visceral leishmaniasis, the Panel recommends deferring treatment of cutaneous leishmaniasis until the postpartum period for most individuals with HIV-cutaneous leishmaniasis **(CIII).** One study suggests that lesions of cutaneous leishmaniasis may be larger and are more likely to be exophytic in pregnancy, and that untreated cutaneous leishmaniasis may be associated with an increased risk of preterm delivery and stillbirth.[120] This is presumed to be related to transient modulation of maternal immune responses during pregnancy.[121] In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, the Panel recommends shared decision making with the patient to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) **(CIII).** Systemic therapy is recommended in most cases of mucosal leishmaniasis in patients with HIV **(CIII).** During pregnancy, when systemic therapy is chosen for mucosal leishmaniasis or cutaneous leishmaniasis, the treatment of choice is liposomal amphotericin B **(CIII).**

Perinatal transmission of *Leishmania spp*. is rare. In a systematic review of suspected cases of vertical transmission, 26 were reported after 6 months postbirth.[109,115,122-124] A case report described a woman with HIV who experienced visceral leishmaniasis relapse during pregnancy and was treated with 40 mg/kg liposomal amphotericin; the infant likely acquired leishmaniasis from amastigotes seen in the placenta.[125]

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