

Leishmaniasis in immunosuppressed individuals

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Abstract

Leishmaniasis is a vector-borne chronic infectious disease caused by a group of protozoan parasites of the genus *Leishmania*. Whereas most immunocompetent individuals will not develop disease after *Leishmania* infection, immunosuppression is a well-established risk factor for disease. The most severe form is visceral leishmaniasis (VL), which is typically fatal if untreated. Whereas human immunodeficiency virus (HIV) co-infection (VL–HIV) was initially mainly reported from southern Europe, it is now emerging in other regions, including East Africa, India, and Brazil. VL has also been found in a wide range of non-HIV-related immunosuppressive states, mainly falling under the realm of transplantation medicine, rheumatology, haematology, and oncology. Clinical presentation can be atypical in immunosuppressed individuals, being easily misdiagnosed or mistaken as a flare-up of the underlying disease. The best diagnostic approach is the combination of parasitological and serological or molecular methods. Liposomal amphotericin B is the drug of choice. Treatment failure and relapse rates are particularly high in cases of HIV co-infection, despite initiation of antiretroviral treatment. Primary prophylaxis is not recommended, but secondary prophylaxis is recommended when the patient is immunosuppressed. Cutaneous leishmaniasis can have a number of particular features in individuals with immunosuppression, especially if severe, including parasite dissemination, clinical polymorphism with atypical and often more severe clinical forms, and even visceralization. Mucosal leishmaniasis is more common. Treatment of cutaneous and mucosal leishmaniasis can be challenging, and systemic treatment is more often indicated. With globally increased travel and access to advanced medical care in developing countries, the leishmaniasis burden in immunosuppressed individuals will probably continue to rise, warranting increased awareness and enhanced surveillance systems.

Keywords: Anti-TNF- α , HIV, immunosuppression, leishmaniasis, transplant, visceral

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Introduction

Leishmaniasis is a chronic infectious disease caused by a group of protozoan parasites of the genus *Leishmania*. The parasites are transmitted to humans via the bite of phlebotome sandflies, and predominantly target reticuloendothelial cells. Leishmaniasis can present with a spectrum of clinical manifestations (Table 1) [1]. Visceral leishmaniasis (VL; kala azar) is a potentially fatal condition characterized by hepatosplenomegaly, chronic fever, weight loss, and pancytopenia [2]. Typically, VL is classified as zoonotic, caused by *Leishmania infantum* (syn. *Leishmania chagasi* in South America), with the dog as the main reservoir, or anthroponotic,

caused by *Leishmania donovani*, mainly found in East Africa and the Indian subcontinent [1–3]. Cutaneous leishmaniasis (CL) is more widely distributed [3,4]. Ulcerative skin lesions occurring at the site of the bite of the sandfly constitute the most common cutaneous manifestation (localized CL). Although it often heals spontaneously, CL typically leaves scars and can be disfiguring and stigmatizing. There are several more rare forms, such as diffuse CL, which is often difficult to treat. Mucosal leishmaniasis (ML) or mucocutaneous leishmaniasis (MCL) refers to an often destructive form with mucosal inflammation, which has been mainly reported in association with *Leishmania braziliensis* [4,5], but also in the Old World [6]. The most recent global estimates suggest

TABLE 1. Aetiology, burden, clinical forms and treatment of leishmaniasis

Aetiology/main geography ^a	High-burden countries	Clinical presentation/forms	Main treatment options
VL <i>Leishmania infantum</i> (syn. <i>Leishmania chagasi</i>): Mediterranean basin, Latin America, Middle East, Asia (China) (zoonotic transmission) <i>Leishmania donovani</i> : Indian subcontinent (anthroponotic), East Africa (mainly anthroponotic; possibly zoonotic transmission) CL and ML New World CL: (South and Central America) <i>Leishmania braziliensis</i> , <i>Leishmania panamensis</i> , <i>Leishmania peruviana</i> , <i>Leishmania guyanensis</i> , <i>Leishmania colombiensis</i> , <i>Leishmania amazonensis</i> , <i>Leishmania mexicana</i> , <i>Leishmania venezuelensis</i> Old World CL: <i>Leishmania major</i> (north-eastern Africa, Middle East, Asia); <i>Leishmania tropica</i> (Asia, North Africa, Middle East); <i>Leishmania aethiopica</i> (Ethiopia); <i>L. infantum</i> (see above)	Top six countries (90% of global burden): India, Nepal, Bangladesh, Brazil, South Sudan, Ethiopia Top 10 countries (70–75% of global burden): Afghanistan, Iran, Syria, Algeria, Ethiopia, North Sudan, Colombia, Brazil, Costa Rica, Peru	Persistent fever, (hepato)splenomegaly and weight loss Pancytopenia, hyperglobulinaemia Localized CL rare forms: Diffuse CL Disseminated CL Leishmaniasis recidivans cutis ML	Antimonials Conventional amphotericin B Liposomal amphotericin B Miltefosine ^b Paromomycin ^b Local treatment: Intralesional antimonials Topical paromomycin Cryotherapy/thermotherapy Systemic treatment: Antimonials Conventional and liposomal amphotericin B Miltefosine ^b Paromomycin ^b Ketoconazole/fluconazole Pentamidine

CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis; VL, visceral leishmaniasis.
^aSome more exceptional species (e.g. *Leishmania killicki*, *Leishmania pifanoi*, and *Leishmania garnhami*) are not included.
^bDifficult to obtain/limited availability in most Western countries.

approximately 0.2–0.4 million annual cases of VL and approximately 1 million cases of CL [3].

Whereas autochthonous leishmaniasis remains relatively rare in Europe, being mainly confined to southern Europe (estimated annual VL incidence of 340–510 cases), imported leishmaniasis is now being increasingly reported [7–12]. As demonstrated by the spread of *L. infantum* in Italy and the recent outbreak in Madrid [13], leishmaniasis has the potential to further emerge or re-emerge within Europe, through spread of the current species (*L. infantum* and *Leishmania tropica*) because of climate change, the introduction of exotic *Leishmania* species because of international travel and immigration, and the increased number of immunosuppressed people [14,15]. Immunosuppression is one of the strongest risk factors for overt clinical disease, and can also alter disease presentation and treatment response. Although immunosuppression has historically been mainly observed in human immunodeficiency virus (HIV)-infected patients, non-HIV-related immunosuppressive conditions are becoming increasingly prevalent globally, mainly because of better medical care of patients with chronic illnesses and the therapeutic use of immunosuppressive drugs. In this review, we focus on the challenges in terms of diagnosis, prevention and treatment of leishmaniasis in immunosuppressed individuals. Given its life-threatening potential and the strong interaction with immunosuppression, the main focus will be on VL.

Epidemiology and Risk Factors

The epidemiological and clinical impact of immunosuppression on VL was most strikingly illustrated by the effect of the

HIV epidemic in VL-endemic countries in southern Europe, with HIV contributing to the re-emergence of VL. By early 2000, almost 2000 cases of VL–HIV (predominantly in intravenous drug users) had been notified, with 50–60% of all VL cases being HIV-co-infected at some point [16]. It is of interest that an anthroponotic transmission cycle for *L. infantum* could be demonstrated, whereby parasites were transmitted among intravenous drug users via the shared use of needles and syringes [17]. Moreover, some studies demonstrated that *L. infantum* could be more readily detected in peripheral blood in HIV-infected patients, suggesting increased infectivity, and possibly also indicating an overall higher parasite load. Fortunately, with the wide-scale introduction of highly active antiretroviral therapy (HAART), a gradual decline in VL incidence has been observed over the last decade [18,19]. Currently, the burden of VL–HIV co-infection is most pronounced in some regions in East Africa, such as north-western Ethiopia, where between 20–40% of individuals with VL are co-infected with HIV [18]. The problem also seems to be emerging in India and Brazil [18,20–23].

In Europe, where individuals with VL–HIV co-infection are often intravenous drug users, parasites causing VL in HIV-infected individuals have been found to be more diverse, with higher enzymatic polymorphism, than those in the general population [16]. In some HIV-co-infected cases, non-human pathogenic trypanosomatids have been isolated [24,25]. The extent and significance of these observations at the global level are currently not well defined. It is of interest that a recent study from Italy suggested an apparent reversal of the initial increase in zymodeme diversity concurrent with HAART introduction [26].

Non-HIV-related immunosuppressive conditions are now attracting increasing attention. This group comprises a heterogeneous collection of medical conditions that hamper VL immunological control and promote either reactivation from a latent infection, or failure to control a new infection. Broadly speaking, the vast majority of reported non-HIV-related immunosuppressive conditions fall under the realm of transplantation medicine, rheumatology, haematology, and oncology. VL has been reported after many different types of organ transplantation [27–36]. Antinori *et al.* provided a detailed review of leishmaniasis in organ transplant recipients, and reported on 79 cases by 2008, a four-fold increase since the early 1990s [31]. Most (77%) were diagnosed after renal transplantation (which is also the most commonly performed procedure). VL was most frequently observed (86% of cases), followed by MCL, and CL was observed more rarely. In this study, the time of occurrence of leishmaniasis tended to vary with the organ concerned, with median times of 6 months after liver transplantation and 19 months after renal transplantation. Several VL cases have been diagnosed after haematopoietic stem cell/bone marrow transplantation [37–40]. With the number of organ or tissue transplantations growing globally, and travel to and from VL-endemic regions becoming more common, the burden will most likely increase [40–42]. Given the lack of detailed prospective studies, data on the risk and determinants of VL across the different types of transplantation and immunosuppressive drugs used are limited.

In the field of rheumatology, VL has been reportedly associated with the use of various immunosuppressive drugs, such as azathioprine, methotrexate, steroids, cyclosporine, and cyclophosphamide (Table 2) [43–49]. The introduction of tumour necrosis factor- α (TNF- α) antagonist drugs has received much attention recently [50]. Whereas initial reports mainly focused on the risk of tuberculosis following the use of these drugs, there are now also a substantial number (several tens) of reports on leishmaniasis, typically occurring after many months of use [51–54]. Although the type was VL in the majority of cases, CL and MCL were also observed. Current data suggest a higher risk in patients receiving anti-TNF- α monoclonal antibodies (such as infliximab) than in patients treated with TNF- α receptor constructs, such as etanercept [51]. As a global surveillance and reporting system is currently lacking, the current numbers are most likely underestimated. A European adverse event reporting system to detect rare infections associated with immunosuppressive and immunomodulatory therapies has been called for [55]. There have also been cases of leishmaniasis in patients receiving chronic steroid treatment for several indications, including asthma, sarcoidosis, and myasthenia gravis [56–58], and receiving other immunosuppressive drugs for a range of conditions, including inflam-

TABLE 2. Selected reports on cases of visceral leishmaniasis found in non-human immunodeficiency virus-related immunosuppressive conditions^a

Medical condition	Immunosuppressive drugs	Reference
Transplantation		
Bone marrow/haematopoietic stem cells	Various, including steroids, cyclosporine, azathioprine, tacrolimus, and mycophenolate mofetil	[37–40,183]
Solid organ: mainly kidney; more rarely liver, heart, lung, and kidney–pancreas		[27–36,184]
Rheumatological/connective tissue diseases/vasculitis		
Rheumatoid arthritis	Various, including steroids, methotrexate, cyclophosphamide, anti-TNF- α agents	[44,46,47,51,98,99,185–189]
Systemic lupus erythematosus		[43,45,99]
Wegener's granulomatosis		[48]
Idiopathic juvenile arthritis		[80,190]
Ankylosing spondylitis		[149,190]
Giant cell arthritis		[149]
Psoriatic arthritis		[51,111,191]
Other chronic inflammatory or iatrogenic immunosuppressive conditions		
Asthma	Steroids	[56]
Asthma/dermatitis	Steroids	[168]
COPD	Steroids	[58]
Cheilitis granulomatosa	Steroids	[56]
Ulcerative colitis	Azathioprine/cyclosporine	[59]
Sarcoidosis	Steroids	[57]
Myasthenia gravis	Steroids	[56]
Oncology		
Haematological malignancies	Various (chemotherapy)	[60,192–195]
Solid tumours		[61]

COPD, chronic obstructive pulmonary disease; TNF- α , tumour necrosis factor- α .
^aNon-exhaustive, with priority given to more recent or particularly interesting cases.

matory bowel disease [59]. Several cancer-related cases (mainly haematological malignancies) of VL have been reported, associated with the use of various chemotherapeutic regimens or monoclonal antibodies [60,61]. Reports of leishmaniasis in patients with primary immunodeficiencies are rare.

That immunosuppressive conditions pose a real challenge in VL-endemic regions is illustrated by the recent *L. infantum* community outbreak in Madrid [13]. Among the 446 cases detected between July 2009 and December 2012, 15.2% ($n = 68$) had immunosuppressive conditions, mostly non-HIV-related. Overall, 31.3% of VL cases and 6.3% of CL cases were diagnosed in immunosuppressed individuals.

Immunology

The immunology and pathogenesis of leishmaniasis are complex; see a number of recent reviews for detailed information [62–64]. In the majority of individuals, *Leishmania* infection does not progress to overt disease. In some highly endemic areas, up to 30% of the inhabitants are asymptotically infected [65]. Although the determinants of progression to disease after primary infection are only partly understood, parasitic virulence, nutritional status, age and host genetic and response factors are known to contribute [63,66]. Control of

infection relies on activated, leishmanicidal macrophages and an intact specific T-helper cell type 1 (Th1) response. A positive leishmanin skin test result is assumed to indicate cell-mediated immunity. Overt disease is associated with a mixed Th1/T-helper cell type 2 (Th2) response. High levels of regulatory T-cells are thought to contribute to the pronounced immunosuppression seen during VL [1]. Important proinflammatory cytokines mediating an effective Th1 response, enhancing the leishmanicidal capacity of macrophages, include interferon- γ and TNF- α . Usually, viable parasites persist after primary infection, and this can potentially lead to reactivation and disease if immunosuppression occurs [18,67].

Whereas CD4 T-cell depletion and skewing towards a Th2 immune response are hallmarks of HIV infection, immune alterations occur at multiple levels of the innate and adaptive immune system, including macrophage dysfunction [68]. Importantly, HIV and *Leishmania* co-localize and interact in the same host cell (macrophages and dendritic cells), mutually reinforcing each other's pathogenic effects and further compromising macrophage function [69]. Clinical data suggest that *Leishmania* co-infection leads to increased immune activation in HIV-infected patients, which persists even after apparently successful VL treatment or after initiation of HAART, potentially leading to further HIV disease progression and a poor CD4 cell count response [70–72]. Whereas most VL–HIV-co-infected patients in Europe present with CD4 cell counts of <200 cells/mL at VL diagnosis [15,68], studies in Ethiopia—where *L. donovani* is prevalent—have demonstrated the occurrence of VL with higher CD4 cell counts [69,70].

The non-HIV-related immunosuppressive conditions predisposing to VL constitute a heterogeneous group of different medical conditions, mostly iatrogenic via immune-ablative chemotherapy, and immunosuppressive or immunomodulatory drugs. For most, different layers of the immune system are affected, and the precise mechanism behind the VL risk has not been well defined. Although most of these conditions will affect other cells and molecules, T-cell lymphocytes are usually significantly affected, through different mechanisms, including lymphocyte depletion, interference with maturation, cell cycling and co-stimulation, and induction of tolerance, thereby altering the mechanisms of defence against intracellular microorganisms [73]. In this scenario, VL can develop because of reactivation from a previous dormant infection, a *de novo* infection when the individual is residing in a VL-endemic area, and very rarely iatrogenic infection via an infected donor organ or blood product [31]. Reactivation is thought to be the most common mechanism causing transplant-related VL in endemic areas, especially those cases occurring relatively early after the intervention, when the immunosuppression is most pronounced [74,75].

Diagnostic Aspects

Clinical presentation and diagnostic challenges

Although most cases of VL–HIV co-infection will show the typical VL signs and symptoms, atypical presentations occur in those who are severely immunosuppressed. Most often, these will consist of (localized) detection of parasites in abnormal tissues such as the intestine, oral cavity, skin, and lung tissue. Skin manifestations appear to be more frequent, and can occur before, during or after the VL episode [76–83]. However, parasites have also been found in healthy skin or coincidentally in other skin pathologies and tattoos [84]. The current data do not allow a reliable comparison with the clinical presentation in individuals with non-HIV-related immunosuppression, but atypical presentations have been reported, and the disease manifestations in those with HIV-related and non-HIV-related immunosuppression are probably similar [85]. In renal patients, VL can lead to graft dysfunction [31].

Post-kala azar dermal leishmaniasis appears to be more frequent in individuals with immunosuppression [86]. Whereas post-kala azar dermal leishmaniasis is usually not seen with *L. infantum*, it has been described in HIV patients [87–92], in some cases being attributed to the immune reconstitution inflammatory syndrome (IRIS) and non-HIV-related immunosuppression.

Symptoms and signs of VL can overlap with those of various conditions, including opportunistic infections. Disseminated mycobacterial infections, lymphoma and disseminated histoplasmosis should be considered in the differential diagnosis. Laboratory abnormalities are also diverse and non-specific, and include, besides pancytopenia, increases in acute-phase response proteins (C-reactive protein, sedimentation rate, and ferritin). VL is also characterized by overactivation of B-cells, leading to pronounced polyclonal hypergammaglobulinaemia, and sometimes producing positive indirect Coombs test results, and detectable levels of anti-nuclear antibodies, anti-dsDNA antibodies, anti-smooth muscle antibodies, anti-cardiolipin antibodies, anti-cyclic citrullinated peptide antibodies, and IgM rheumatoid factor [93]. Activation of the coagulation cascade (increased D-dimer levels, decreased fibrinogen levels, prolonged prothrombin time, and prolonged activated partial thromboplastin time), circulating immune complexes, low complement levels and cryoglobulinaemia have also been observed [94–96]. There are several reports of VL resembling or initially being misdiagnosed as an autoimmune disease (including systemic lupus erythematosus and rheumatoid arthritis), or as a flare-up of the underlying disease [43–49,97–99], and this can potentially lead to inappropriate increases in immunosuppressive drug use [43–45,49,100] or

even unnecessary splenectomy [98]. There have been cases of rheumatoid arthritis in patients receiving anti-TNF- α therapy, whereby VL was misdiagnosed as drug-induced lupus [101,102]. Similarly, the combination of pancytopenia, splenomegaly and abnormalities on bone marrow biopsy has led to misdiagnosis as (mainly haematological) malignancies [61,103,104]. The haemophagocytic syndrome also has several features that are similar to those of VL (including fever with pancytopenia, hepatosplenomegaly and a pronounced pro-inflammatory cytokine burst), but VL can also act as an infectious trigger for a secondary haemophagocytic syndrome, with pronounced haemophagocytosis being seen in the bone marrow [105,106]. Other reports of challenging VL diagnosis include presentation as a monoclonal gammopathy [107] and autoimmune hepatitis [100,108,109].

Laboratory diagnosis

Microscopy for parasite detection in different tissue samples is highly specific and achieves good sensitivity, including in immunocompromised patients, but the performance strongly depends on the experience of the microscopist. In HIV-infected patients, microscopy on spleen tissue is considered to have the highest sensitivity (Table 3) [18]. In a systematic review by Antinori *et al.* [31], the sensitivity of bone marrow microscopy was estimated to be 81% in HIV-positive patients and 98% in transplant patients. Nevertheless, a negative bone marrow (or spleen) aspiration finding does not completely rule out VL, and there are several reports in which VL was diagnosed only after repeat bone marrow examination [110,111]. Culture can further increase sensitivity, and allows species identification, but can take several weeks; microculture appears to be faster [112]. Importantly, microscopy or culture

on peripheral blood or buffy coats can also contribute to diagnosis, with the sensitivity of microscopy of blood smear staining estimated to be approximately 50% in HIV-infected patients [18,113]. High parasitaemia is not common in immunocompetent individuals in the Mediterranean endemic areas, and should raise the suspicion of associated immunosuppression [114].

Serological tests for VL diagnosis, such as the indirect fluorescent antibody test, are very useful in immunocompetent patients, particularly in paediatric cases [115]. In resource-constrained settings, the direct agglutination test and the rK39 rapid diagnostic test are most commonly used [18]. Serological tests are clearly less reliable in HIV-infected patients [18,116]. In Europe, they were found to present much lower levels of *Leishmania*-specific serum antibodies, and >40% of VL-HIV-co-infected patients can be negative by serology [117]. The experience with the direct agglutination test in East Africa seems to be better, with a sensitivity of >80% [118]. Unlike in HIV-infected patients, the diagnostic sensitivity of serological tests in other immunocompromised patients, such as those receiving solid organ transplants, appears to be good. In the study by Antinori *et al.* [31], the sensitivity of the indirect fluorescent antibody test was estimated to be 48% in HIV-infected patients but 93% in transplant patients. Serology also appears to be useful for the diagnosis of VL in patients receiving anti-TNF- α therapy [47].

Molecular diagnosis with PCR, using both bone marrow and peripheral blood samples, is highly sensitive and specific for the diagnosis of VL in HIV-infected patients. Furthermore, a recent comparative study of parasitological, serological and molecular tests for VL in HIV-infected patients demonstrated that the sensitivity of PCR in blood samples was as good as that of

TABLE 3. Overview of the main diagnostic methods used and their performance in immunosuppressed individuals.

Technique	Tissue/fluid	Immunosuppression	Sensitivity (%)	Invasiveness	Feasibility (field use)	Reference
Microscopy	Blood	HIV	50	+	+	[18]
	Spleen	HIV	>95	+++	+	[18]
	Bone marrow	HIV	67–94	++	+	[18]
	Lymph node	HIV	53–65	++	+	[196]
	Bone marrow	SOT	98	++	+	[31]
	Bone marrow	Other	100	++	+	[85]
Culture	Bone marrow	HIV	70–81.3	++	+	[31,197]
		SOT	82.0	++	+	[31]
	Blood	HIV	67	+	+	[113]
IFAT	Serum	HIV	48–75	+	+	[117,197]
		SOT	92	+	+	[31]
		Other	100	+	+	[85]
DAT	Serum	HIV	87.80	+	++	[198]
PCR	Blood	HIV	72–100	+	+	[121,122,199,200]
	Bone marrow	HIV	82–100	++	+	[121,122,199,200]
Latex agglutination test	Urine	HIV	48–85.7	–	++	[124,201]
rK39 dipstick	Serum	HIV	46.6–93.9	+	++	[198,202]

DAT, direct agglutination test; HIV, human immunodeficiency virus; IFAT, indirect fluorescent antibody test; SOT, solid organ transplant.

direct examination of bone marrow aspirates [118]. There is also a general consensus that PCR on blood samples is the most useful technique for monitoring the long-term efficacy of drug therapy and for identifying relapses in treated patients, avoiding repeated invasive procedures. Typically, conventional *Leishmania* PCR on blood will become negative early after the beginning of treatment; reappearance of a positive PCR could indicate (or predict) relapse. With quantitative PCR, thresholds have been identified, predicting the onset of symptoms and the development of VL relapse [119–122]. Although these have most commonly been used in HIV-infected patients, this approach also appears to be useful in other immunosuppressive conditions [31], and should probably be recommended for monitoring treatment response in patients with immunosuppression.

One more option for VL diagnosis is the latex agglutination test for the detection of leishmanial antigen in the urine. Although this is rapid, non-invasive, and simple, the sensitivity is low to moderate in immunocompetent individuals [123]; however, in HIV-infected patients, sensitivity up to 85.7% was found during a primary episode of VL [124]. Although reports are lacking, this method might also be useful for diagnosing VL in transplanted patients.

In conclusion, taking into account the different performances of the diagnostic tests for VL in immunocompromised individuals, the variability of disease presentation, and the different conditions of the patients, the best approach for diagnosis of VL is the combination of parasitological and

serological or molecular methods, possibly to be repeated if initial results are negative but clinical suspicion remains.

Treatment

Substantial experience has accumulated with regard to the treatment of VL in HIV-co-infected individuals, both within and outside Europe (mainly in Ethiopia) [18]. In general, HIV co-infection is associated with higher initial failure and relapse rates, more drug toxicity, and higher treatment-associated mortality [18]. Particularly with antimonials, enhanced and potentially life-threatening toxicity is observed in patients with HIV co-infection. Given their excellent safety profile, the current WHO and international guidelines—mainly based on evidence from European studies—recommend liposomal amphotericin B as the preferred treatment (Table 4) [125–128]. The WHO proposes a total dose of 40 mg/kg [125–127], but lower doses might be possible in India [129]. Experience with miltefosine is limited, with available studies suggesting moderate efficacy and an acceptable toxicity profile [130–133]. Repeated VL episodes in HIV-infected patients tend to become progressively more difficult to treat, and are often associated with poor CD4 recovery; hence, preventing VL relapse is key. This provides the rationale for effective treatment of (primary) VL, followed by timely initiation of HAART and secondary prophylaxis (see below). The role of combination therapy in patients with VL–HIV co-infection remains to be explored

TABLE 4. Treatment recommendations for leishmaniasis in immunosuppressed individuals.

Organization	Target group	Preferred therapy	Alternative therapy
VL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Liposomal amphotericin B 21 mg/kg total dose 3 mg/kg IV days 1–5, 14, 21	Amphotericin B deoxycholate 1.0 mg/kg daily for 15–20 days or a pentavalent antimony compound ^a
Centers for Disease Prevention and Control [128]	HIV	Liposomal amphotericin B 20–60 mg/kg total dose 2–4 mg/kg IV daily or interrupted schedule (e.g. 4 mg/kg days 1–5, 10, 17, 24, 31, 38)	Other amphotericin B lipid complex dosed as for liposomal amphotericin B Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily (total dose of 1.5–2.0 g) SSG 20 mg Sb5+/kg IV/IM daily for 28 days Miltefosine 100 mg PO daily for 4 weeks
Food and Drug Administration [126]	Immunosuppression (HIV and non-HIV)	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV days 1–5, 10, 17, 24, 31, 38	
WHO [127]	HIV	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV daily or days 1–5, 10, 17, 24, 31, 38	
CL and MCL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Pentavalent antimonials ^a 20 mg Sb5+/kg IV/IM daily CL: 21 days MCL: 28 days	Conventional or liposomal amphotericin B, miltefosine, paromomycin, pentamidine, and fluconazole, based on species and availability
Centers for Disease Prevention and Control [128] (only for CL, not for MCL/ML)	HIV	Liposomal amphotericin B as for VL SSG 20 mg Sb5+/kg IV/IM daily for 28 days	Miltefosine PO, topical paromomycin, intralesional SSG, or local heat therapy

CL, cutaneous leishmaniasis; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; MCL, mucocutaneous leishmaniasis; PO, per os; SSG, sodium stibogluconate (pentavalent antimony); VL, visceral leishmaniasis.

^aStibogluconate or meglumine antimoniate.

[134]. Although efficacy data are lacking, many experts are in favour of combined therapy for patients with multiple relapses.

VL is an AIDS-defining condition, requiring HAART irrespective of CD4 counts [127]. Although there are data suggesting that HIV-1 protease inhibitors might directly exert inhibitory effects against *Leishmania*, there is insufficient evidence for their clinical use against VL, and standard HAART regimens are currently recommended [135]. In contrast to many other HIV-associated opportunistic infections, IRIS appears to be relatively rare [136]. Although the widespread use of antiretroviral treatment has resulted in dramatic reductions in the incidence of VL-HIV co-infection, the effect on relapse is only partial, and 1-year relapse rates of 30–60% have been reported [18,137]. Established risk factors for VL relapse include a previous episode of VL, low CD4 counts, and the lack of secondary prophylaxis [138].

Most evidence regarding secondary prophylaxis stems from retrospective observational studies in European HIV-infected patients receiving either antimonials, lipid formulations of amphotericin B, or pentamidine, administered every 2–4 weeks. There is limited experience with the use of miltefosine [132,139]. Only one small randomized controlled trial on secondary prophylaxis has been published. In the eight patients receiving amphotericin B lipid complex (administered as 3 mg/kg every 3 weeks), the 1-year relapse rate was 50%. This compared favourably with the 78% relapse rate in the nine patients without prophylaxis [140]. Whereas maintenance therapy is generally recommended for those at risk of VL relapse in areas with zoonotic VL, such as Europe, this remains controversial in areas with human-to-human transmission, owing to the risk of rapid spread of drug resistance [18,127,128]. Nevertheless, also in such a setting, clinicians have used secondary prophylaxis on a case-by-case basis.

The experience with non-HIV immunosuppressive conditions is more fragmented, and is mostly based on case reports or small case series. Although no firm conclusions can be drawn, the current data seem to suggest that initial treatment response is better and recurrence rates are lower than in HIV-infected individuals, but not as good as seen in the immunocompetent population. For instance, Antinori *et al.* reported an initial cure rate of 84% in transplant patients, which was better than in HIV-infected patients (55–66%) but not as good as in immunocompetent individuals (93–97%). Nevertheless, mortality was substantial (15/79; 22%), although this included five patients who did not receive VL treatment but had the diagnosis revealed by autopsy [31]. Relatively high rates of potentially fatal toxicity were seen with antimonials [31,58]. Although systematic comparisons are lacking, most authors recommend liposomal amphotericin B, because of its good safety profile [31,125,141] (Table 4). Treatment can be

complicated by overlapping toxicity and drug interactions between some anti-leishmanial and immunosuppressive drugs [31]. A few renal transplant patients have been successfully treated with fluconazole or ketoconazole, combined with allopurinol [142–145]. The indications for secondary prophylaxis remain to be defined [31,125,141], but prophylaxis has, up to now, only been exceptionally used in patients with non-HIV-related immunosuppression [7,31]. Perhaps surprisingly, many patients remained relapse-free without maintenance therapy and despite the ongoing use of immunosuppressive medication, although dose reduction was often instituted, at least temporarily [146].

Prevention

As there is no vaccine available for human leishmaniasis, strategies for early detection have to be considered. Transplant donor screening for leishmaniasis is currently not suggested in most guidelines or recommendations [74,141,147]. Serological screening of transplant recipients with a history of potential exposure to *Leishmania* may be considered before transplantation [75,141], although the evidence base is limited [74]. Others have argued more strongly in favour of screening prior to the initiation of immunosuppressive treatment of any kind, proposing either serology, skin testing or PCR as a screening tool [28,32,37,38,148–151], possibly even at regular intervals. As is the case for tuberculosis, *Leishmania*-specific interferon- γ release assays have been developed, and could be used for screening purposes [152–156]. If an immunosuppressed individual is known or found to be asymptotically infected or has a history of VL, close monitoring is warranted [74,141]. Besides regular clinical evaluation, some authors have argued for additional regular laboratory evaluation with PCR [32]. Although pre-emptive treatment in immunosuppressed patients has been proposed for Chagas disease [157], such strategies have not yet been explored for VL. Primary prophylaxis for VL in asymptotically infected individuals (similar to isoniazid preventive therapy in those with a positive tuberculosis skin test result) is currently not recommended [127]. It is of interest that, in a recent Brazilian study, none of the liver transplant recipients who were found to be *Leishmania*-PCR positive at the time of transplantation or received a PCR-positive organ developed VL over a median follow-up of 24 months, without any prophylaxis being given [158]. Obviously, protective measures to prevent exposure to sandfly bites are recommended for immunosuppressed individuals living in or travelling to *Leishmania*-endemic regions [7]. With regard to HIV-infected patients, VL screening or primary

prophylaxis is not recommended in international guidelines [127,128]. However, this has never been well studied, and merits further exploration in VL-endemic areas.

CL and ML

A vast number of cases of CL and ML have been reported in immunosuppressed individuals. Besides series of HIV-infected patients [18,159] and transplantation cases [31,160–162], there are also reports of reactivation of infection after initiation of immunosuppressive drugs such as anti-TNF- α agents [163–165] and steroids [51,166–168]. Although the clinical presentation will often be similar to that in immunocompetent individuals, a number of particular features have been reported, especially in cases of severe immunosuppression. These include parasite dissemination, and clinical polymorphism with atypical and often more severe clinical forms [18,20,169–171]. Immunosuppression is a risk factor for diffuse CL, an anergic form that is notorious for its poor treatment response [76,172]. In this form, multiple nodular lesions containing large numbers of parasites are seen (Fig. 1). Disseminated CL, presenting with multiple pleomorphic lesions, is another rare form that can be seen in immunodeficient and immunocompetent individuals. ML and MCL appear to be more common in immunosuppressed patients [6,170,173]. Whereas MCL is typically associated with *L. braziliensis*, there are increasing reports of mucosal



FIG. 1. Diffuse cutaneous leishmaniasis in a transplant patient, caused by *Leishmania infantum* acquired in Spain.

lesions (with or without concurrent cutaneous or visceral disease) caused by *L. infantum*/*L. donovani*, *Leishmania major*, and *L. tropica* [6]. In several cases, isolated ML was initially diagnosed (and treated) as malignancy or vasculitis. As in immunocompetent individuals, diagnosis of CL and ML relies on tissue sampling, but there is a long list of differential diagnoses in immunosuppressed patients. Visceralization of dermatotropic species has been reported, besides skin dissemination of viscerotropic species [35,174,175]. There have been reports of CL-related IRIS, with HAART unmasking or exacerbating CL, in some cases with associated eye infection [176].

As the recommended treatment of CL varies by species, species identification should be pursued. There are several excellent reviews providing detailed information on the treatment of CL, predominantly focused on immunocompetent patients and/or travellers [5,125,177–181]. Given the lack of evidence, it is unclear to what extent treatment guidelines should differ for immunodeficient individuals [163]. Especially with advanced immunosuppression, treatment response can be poorer, with higher rates of recurrence, and the risk of dissemination and concurrent VL and ML is higher. Generally speaking, immunosuppression (especially if severe) is a factor arguing in favour of systemic treatment instead of local therapy for CL [125]. Importantly, concurrent VL and ML will have to be looked for. The evidence base for the treatment of ML and MCL is limited, and this is even more the case for immunosuppressed individuals. Although some cases of isolated ML have been successfully treated with local treatment, most authors argue in favour of systemic treatment for ML, given the risk of subsequent visceralization [173,182]. Table 4 summarizes some recent recommendations.

Conclusion

Both HIV-related and non-HIV-related immunosuppression pose significant challenges for the diagnosis and management of VL and, to a lesser extent, CL. Whereas HIV-associated VL was reported frequently in southern Europe before the introduction of HAART, VL is now more often seen in patients with non-HIV-related immunosuppression. As not all cases are reported or notified, the current burden of leishmaniasis in immunosuppressed individuals is probably underestimated. At the global level, the burden of both HIV-related and non-HIV-related immunosuppressive leishmaniasis will probably continue to rise, owing to globally increased travel and access to advanced medical care. This warrants increased attention and enhanced surveillance

systems. Early diagnosis will require increased awareness among the medical community across various disciplines, and the wide availability of or access to accurate diagnostic tools. The value and cost-effectiveness of screening and prophylactic treatment merits further research.

Author Contributions

J. van Griensven: developed the outline of the paper, reviewed the literature, and wrote the first draft. E. Carrillo and J. Moreno: contributed the section on laboratory diagnosis. E. Carrillo, R. López-Vélez, L. Lynen and J. Moreno: reviewed subsequent drafts. All authors read and approved the final manuscript. Fig. 1 was provided by R. López-Vélez.

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Transparency Declaration

Nothing to declare.

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