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# Pharmacological Approaches to Visceral Leishmaniasis in Patients with Immunocompromised Status

## İmmün Yetmezlik Durumu Olan Hastalarda Visseral Leishmaniasise Farmakolojik Yaklaşımlar

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## Abstract

Visceral leishmaniasis (VL) is a chronic parasitosis which is hypoendemic in the Mediterranean area but hyperendemic in areas such as Bihar, Sudan, and Northeastern Brazil. *Leishmania donovani* and *Leishmania infantum* are the main etiological agents. After infection by vectors (phlebotomine sandflies), VL symptoms range from a low-symptomatic disease to a rapidly evolving severe syndrome. When VL affects immunocompromised adults, the infection frequently appears paucisymptomatic or as an insidious clinical manifestation with atypical signs and low-grade fever. Patients with human immunodeficiency virus (HIV) infection and organ-transplant recipients have an increased risk of VL and HIV/VL coinfection, which is worrying risk factor in Southwestern Europe and many hyperendemic areas. The availability of effective therapies is limited, and the prognosis of the patients with immunocompromised status is unpredictable. Compared with other therapies, treatment based on the use of liposomal amphotericin B is associated with a lower incidence of side effects, but the cost precludes its use in low-income countries. Antimonials are the longest-used drugs. However, adverse reactions are common, and the mechanisms of resistance to this class of drugs have been enhanced. Miltefosine, the only oral drug available, has uncertain effectiveness against *L. infantum* infection. Data about the efficacy of paromomycin are also limited. Relapses and resistance to drugs are observed in patients with VL/HIV coinfection.
**Keywords:** Visceral leishmaniasis, immunocompromised patients, drugs

## Öz

Visseral leishmaniasis (VL), Akdeniz bölgesinde hipoendemik olan ancak Bihar, Sudan ve Kuzeydoğu Brezilya gibi bölgelerde hiperendemik olan kronik bir parazitozdur. *Leishmania donovani* ve *Leishmania infantum* ana etiyolojik ajanlardır. Vektörler (flebotomin tatarcıkları) tarafından enfeksiyon bulaştırıldıktan sonra, VL'nin şiddeti hafif semptomatik bir hastalıktan hızla gelişen ciddi bir sendroma kadar değişebilir. Visseral leishmaniasis bağışıklığı baskılanmış yetişkinleri etkilediğinde, enfeksiyon sıklıkla pausisemptomatik seyreder veya atipik belirtiler ve düşük dereceli ateşle birlikte

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## Öz

sinsi bir şekilde prezente olur. İnsan immün yetmezlik virüsü (HIV) enfeksiyonu olan hastalarda ve organ nakli alıcılarında, Güneybatı Avrupa'da ve birçok hiperendemik bölgede endişe verici bir risk faktörü olan VL ve HIV/VL koenfeksiyonu riskinde artış bildirilmektedir. Etkili tedaviler sınırlıdır ve bağışıklığı baskılanmış durumdaki hastaların prognozu tahmin edilemez. Diğer tedavilerle karşılaştırıldığında, lipozomal amfoterisin B (L-AmB) kullanımına dayalı tedavi, daha düşük yan etki insidansı ile ilişkilidir, ancak maliyeti düşük gelirli ülkelerde kullanımını engellemektedir. Antimonlar en uzun süre kullanılan ilaçlardır. Bununla birlikte, advers reaksiyonlar yaygındır ve bu ilaç sınıfına karşı direnç mekanizmaları güçlenmiştir. Mevcut tek oral ilaç olan Miltefosin, *L. infantum* enfeksiyonuna karşı belirsiz bir etkiye sahiptir. Paromomisinin etkinliği hakkındaki veriler de sınırlıdır. VL/HIV koenfeksiyonu olan hastalarda nüksler ve ilaçlara direnç gözlenir.
**Anahtar Kelimeler:** Visseral leishmaniasis, bağışıklığı baskılanmış hastalar, ilaçlar

## Introduction

Visceral leishmaniasis (VL) is a parasitosis hypo-endemic in the Mediterranean area but a major threat in some hyperendemic areas such as Bihar, Sudan, and Northeastern Brazil[1]. According to the World Health Organization (WHO), 30,000 new cases of VL are recorded annually, with an estimated mortality of 20,000-50,000 patients annually[2]. Even though synanthropic and domestic mammals act as hosts or reservoirs of several *Leishmania* spp., humans can be the main reservoir of *Leishmania* in some hyperendemic areas. *Leishmania donovani* and *Leishmania infantum* (synonymous with *Leishmania chagasi*) are the etiological agents of VL, which is a major health problem in low-income countries and individuals with immunocompromised status[3,4]. Humans can be infected after an infected vector bite (phlebotomine sandflies), with consequent wide spectrum of symptoms, ranging from a low-symptomatic disease to a rapidly evolving severe syndrome[5]. VL affects mainly children and adults with immunocompromised status, who report frequently a paucisymptomatic infection, with low-grade fever, and insidious clinical manifestations[6]. Leishmania can infect different cells, such as hematopoietic and non-hematopoietic fibroblasts. Indeed, VL should be suspected when unexplained pancytopenia and splenomegaly are reported in a patient with chronic fever[7]. Several risk factors can facilitate the spread of VL; particularly, i) poor socioeconomic conditions, ii) malnutrition, iii) climate, and iv) environmental factors are recognized to increase the risk of a symptomatic infection[5]. Patients with human immunodeficiency virus (HIV) infection and organ-transplant recipients represent the highest-risk categories[8-10]. Patients with hematologic or oncologic malignancies are likely to experience several infections including VL[11]. Moreover, patients with rheumatologic diseases receiving biologic/biotechnological immunomodulating therapy are also at risk of developing infection. Both steroids and conventional disease-modifying antirheumatic drugs (cDMARDs), such as methotrexate, azathioprine, and cyclosporine, as well as biological DMARDs, such as tumor necrosis factor-α (TNF-α) antagonists, impair macrophage function possibly leading to an inability to contain *Leishmania* replication[12,13]. Predisposition to VL infection and progression from infection to overt disease is not clearly explained. After *Leishmania* reaches the bloodstream, it causes both a Th1-adaptive immune response and an innate immune response, mediated by TNF-α and interferon gamma; the inability to start such an immune response causes an overt disease, where a mixed Th1/Th2 response appears to be a crucial pathway in triggering VL manifestations, as is largely reported in patients with immunocompromised status[7]. VL laboratory abnormalities include hypergammaglobulinemia, sometimes coupled with the presence of anti-dsDNA or anti-nuclear antibodies, and low white blood cell, erythrocyte, and platelet counts. Laboratory diagnosis is mainly based on the detection of parasites on the bone marrow or spleen aspirates through microscopy[6,14]. This literature review aimed to summarize the main aspects of VL treatment, focusing on the most investigated drugs and considering new therapeutic approaches.

### Antileishmanial Agents

Several antileishmanial agents can be administered to patients with VL, and many of these drug were not discovered after a specific research in the field of *Leishmania*. The efficacy of the different drugs can vary according to the *Leishmania* species and nutritional and immunologic status. Drugs currently administered to patients with VL demonstrate different profiles of efficacy, administration, and costs. Three drugs are administered intravenously (IV; sodium stibogluconate, amphotericin B deoxycholate (d-AmB), and liposomal amphotericin B [L-AmB]), one orally (miltefosine), and one intramuscularly (IM) [paromomycin (PM)].

### Antimonials

Pentavalent antimonials (i.e., sodium stibogluconate and meglumine antimoniate) at a dosage of 20-40 mg/kg/day for 28-30 days, administered IM or IM, have been used for over 70 years; however, their efficacy has been demonstrated to be lower than that of L-AmB, and toxicity is common (Table 1)[15]. Antimonial pharmacodynamic is not widely understood: after parasites are phagocytosed in the reticulo-endothelial system cells, these drugs

interfere with the *Leishmania* metabolism through the selective inhibition of glycolysis and β-oxidation (phosphofructokinase and pyruvic dehydrogenase), with a consequent reduction in the production of adenosine triphosphate and guanosine-5′-triphosphate[16]. Antimony-resistant phenotype can be associated with genetic variations, i.e., copy-number variations, frameshift mutations in protein-coding genes and non-coding gene mutations, and downregulated/upregulated molecules at the proteomic analysis[17,18]. Response to sodium stibogluconate can be predicted by Programmed death-ligand 1 expression, and further studies are ongoing about the role of this biomarker in VL and other diseases whose clinical expression is mediated by immune system dysregulation[19,20]. Innate drug modulation and host immune-suppressive cytokine expression are related to drug resistance to *L. donovani*[21]. Several mechanisms have been proposed to explain resistance to antimonials. An upregulation of multidrug-resistant protein-1, which lead to the efflux of antimonials, may be determined by IL-10; moreover, microRNAs (miRNAs), such as miRNA-Ago2 or miRNP complex and its antagonist RNA-binding protein HuR, play pivotal roles in macrophage-controlling cytokine production and in the host ability in controlling *Leishmania* replication[22].

Apart from the threats related to antimonial efficacy, adverse drug reactions (ADRs) can limit antimonial success rate in patients with VL. Vomiting, increased liver enzymes, altered electrolyte, and pancytopenia are reported. Pancreatitis leading to treatment discontinuation and death seriously causes electro-cardiac alterations (arrhythmias, Q-T prolongation, and sudden death), and the aforementioned ADRs make antimonial use challenging, especially in high-income areas where patient monitoring can be difficult (Table 2)[23-25]. Antimonials are demonstrated to be unsafe, as they increase the mortality rate by six times compared with miltefosine, and one-third of patients with HIV coinfection who undertake sodium stibogluconate, as part of a study evaluating different formulation efficacies of this drug in Ethiopia, died[26]. In a Spanish study performed in the pre-HAART, most patients with HIV coinfected with *Leishmania* (HIV/VL) showed remission after antimonial treatment, even if recurrence was observed in most cases[27]. Only a 50% clinical and parasitological response to antimonials was observed in a French study conducted in patients with HIV/VL coinfection; indeed, in India, which was reported to have a high rate of resistance to this therapy, therapeutic failure could be even higher[28,29]. In any case, in evaluating the efficacy of each drug in HIV/*Leishmania* coinfection, we should consider the ongoing HIV-specific treatment. Antimonial administration in patients with immunocompromised status can be difficult because it has lower efficacy than L-AmB, and the side effects of many HIV drugs and immunosuppressive drugs frequently overlap those of antimonials. Comparative trials in immunocompromised HIV-negative cases are lacking; however, current data suggest that side effects and increased toxicity can be barriers to antimonial administration at least in developed countries. Instead, data regarding patients with HIV infection suggest that the use of meglumine antimoniate can be associated with a high dropout rate, probably related to the longer treatment period[25].

### AmB

AmB is an antimycotic polyene macrolide produced from actinomycete *Streptomyces nodosus*, which acts as a powerful leishmanicide. AmB binds to ergosterol, the principal membrane sterol of both *Leishmania* and fungi, forming pores on the membrane, which causes parasitic death due to the loss of intracellular potassium and magnesium. Moreover, AmB induces oxidative damage in cells. Although AmB affinity for ergosterol is ten times higher than that for cholesterol, its action on cholesterol makes it toxic, especially on renal function[30]. D-AmB is active in the treatment of VL, but it is difficult to tolerate, as it needs a prolonged treatment time (up to 30 days) and has a

**Table 1. Treatment regimens, recommendations, and efficacy of antileishmanial agents**

| Drug | Dose | Recommendation | Efficacy |
|---|---|---|---|
| L-AmB | 3 mg/kg/day on days 1-5, 14, and 21 (total dose 21 mg/kg) | Principal | High |
| L-AmB sustained by *L. infantum* | 3 mg/kg/day on days 1-5 and 10 | Principal | High |
| L-AmB in India (endemic region) | 10 mg/kg one time or 3 mg/kg, days 1-5 | Principal | High |
| Amphotericin B deoxycholate | 1 mg/kg × 15 doses given qod[†] or qd[†] | Principal | Moderate |
| Miltefosine | 50 mg bid for 28 days if 30-45 kg; 75 mg tid for 28 days if >45 kg | Alternative | High (*L. donovani*); failure (*L. infantum*) |
| Antimonials | 20-40 mg SbV[§]/kg/day for 28 days | Alternative | L-AmB > antimonials |
| Paromomycin | 15 mg/kg up to 21 days | Alternative | Low as monotherapy/in patients with VL/HIV coinfection |

L-AmB: Liposomal amphotericin B, [†]qod: alternate day; [†]qd: daily; [§]SbV: Sodium stibogluconate

relatively high cost in low-income countries. Attention should be paid to the occurrence of ADRs: hemoglobin, kalemia, and azotemia should be checked for drug accumulation toxicity[31]. D-AmB is currently recommended at the dosage of 0.75-1 mg/kg/day along a 15-20-day period, if VL is caused by *L. donovani*, or for up to 30 days if caused by *L. infantum* (Table 1)[16]. The main ADRs include infusion-related events (such as fever, vomiting, hypotension, and tachypnea), severe electrolyte abnormalities, nephrotoxicity, and anemia (Table 2)[32].

### L-AmB

Lipidic formulation has been proposed to reduce side effects of AmB, finally targeting infected cells and reducing toxicity. The administration of a higher dose of L-AmB is the most effective therapy in developed countries, and it reports the highest cure rate (95%) and relatively low toxicity (Table 1)[33]. Indian VL is more responsive than Brazilian and Sudanese VL to the treatment with L-AmB, although in all these regions the high cost of treatment makes its routinary use unaffordable[34]. In a three-arm study conducted in India, which aimed to compare the efficacy of different formulations of AmB, L-AmB demonstrated a lower rate of infusion-related reactions compared with d-AmB. Moreover, although similar cure rates were obtained for those receiving L-AmB, as compared with those receiving AmB lipid complex, fewer infusion reactions and faster time to defervescence were observed after L-AmB administration[35]. High cure rates can be obtained after administration of a short-course regimen (6 doses administered at days 1-5 and 10) at a dosage of 3-5 mg/kg[36]. Single-dose L-AmB at a dosage of 10 mg/kg in VL caused by *L. donovani* or 5 mg/kg L-AmB in combination with miltefosine or PM appears to be effective and can be proposed in highly endemic low-income countries as part of the WHO-guided programs[37]. The current L-AmB regimen in patients with immunocompromised status is based on a therapeutic scheme consisting of 3 mg/kg/day on days 1-5, 10, 17, 24, 31, and 38, with a total dose of 40 mg/kg, as highlighted by the current Infectious Diseases Society of America (IDSA) guidelines[33]. A retrospective study involving patients without HIV infection diagnosed with Mediterranean VL demonstrated that L-AmB should be considered the therapy of choice for VL in adults compared with antimonials, as it allows faster normalization of clinical and laboratory findings, has fewer treatment failures, and has lower toxicity, and the high cost of L-AmB is balanced by the reduction of the length of hospital stay[38]. In a patient with VL, immunocompromised status, and splenectomy, whose diffusion was demonstrated within the liver, bone marrow, lymph nodes, and gastrointestinal tract, L-AmB treatment led to an apparent clinical improvement, followed by VL relapse with severe clinical symptoms. Combined administration of L-AmB, meglumine antimoniate, and pentamidine isethionate resulted in a definitive cure[39]. The results of a study on Sudanese patients suggested that higher doses of L-AmB should be used in patients with coninfections (VL/HIV and VL/tuberculosis coinfections)[40]. In Europe, some patients with coinfection treated with a total dose of L-AmB up to 30-40 mg/kg tolerated the therapy well[41]. In two patients with VL/HIV coinfection resistant to antimony, definitive cure was achieved after L-AmB administration, with no relevant toxicity[42]. Prolonged high-dose administration is required to ensure that resistant parasites are not selected, considering that the accumulation of L-AmB in the spleen, liver, and bone marrow lasts 2-3 weeks[43]. A retrospective study described diagnostic and therapeutic management of 30 renal transplant recipients from endemic regions, who experienced VL in the post-transplantation period. Treatment with L-AmB resulted in an 80% remission rate[44]. WHO and many international guidelines recommend the use of L-AmB in patients with VL/HIV coinfection based on evaluations related to its safety profile and efficacy, even if failure or relapse can be reported in patients with VL/HIV coinfection receiving antiretroviral treatment[6].

**Table 2. Adverse drug reactions and toxicity related to antileishmanial agents**

| Drug | Adverse drug reactions | Toxicity |
|---|---|---|
| L-AmB | Infusion-related fever/chills, nausea/vomiting or diarrhea, rash, back pain, and increased creatinine | Nephrotoxicity less than amphotericin B |
| Amphotericin B deoxycholate | Infusion-related events (fever, vomiting, hypotension, tachypnea), severe electrolyte abnormalities, and anemia | Nephrotoxicity |
| Miltefosine | Nausea/vomiting/diarrhea, headache, motion sickness, increased creatinine, or liver function tests | Nephrotoxicity, hepatotoxicity, and teratogenicity |
| Sodium stibogluconate (antimonial) | Abdominal pain, hyperamylasemia, arthralgias/myalgias, fatigue, headache, nausea/vomiting, fever, arrhythmias, Q-T prolongation, increased liver function tests, thrombocytopenia/leukopenia/ pancytopenia, and altered electrolytes | Hepatotoxicity, pancreatitis, and sudden death |
| Paromomycin | Allergic reactions | Nephrotoxicity, ototoxicity, and curative effect at high doses |

L-AmB: Liposomal amphotericin B

Treatment with L-AmB was successful in several clinical settings involving patients with immunocompromised status, such as in the case of VL in a young man who underwent splenectomy, who had β-thalassemia and chronic hepatitis, treated with pegylated interferon alpha, and in patients with VL and cirrhosis who were admitted for decompensation and fever, in which clinic and laboratory improvement was reported[45,46]. L-AmB therapy has also been shown to be effective and safe in cases of VL in pregnant women without HIV infection, as demonstrated in a case series where such a treatment achieved these benefits without fetal toxicity in five women who presented with fever and hepatosplenomegaly[47].

Relationships between VL and immunosuppressive drugs or HIV-positive status are complex in endemic areas, as we have to consider that, in these settings, detection of *Leishmania* is not always associated with an overt disease and no consensus about prophylactic treatment has been obtained. In any case, we should consider low toxicity drugs with lower effects on the drug-drug interactions for these patients. As reviewed by Ossandon et al.[48,49], 2 of 6 cases retrieved by literature analysis of cases with systemic lupus erythematosus and VL receiving antimonials reported an unfavorable outcome[48]. Apart from these experiences, antimonial use is rarely reported in patients with immunocompromised status without HIV infection. L-AmB, which is the drug used with the highest frequency, reports the highest cure rate[49].

Based on the evidence deriving by literature analysis, L-AmB should be considered the treatment of choice for patients with immunocompromised status considering its efficacy and tolerability profile.

**Paromomycin**

Paromomycin (or aminosidine), first utilized in Kenya, India, and Sudan in the early 1990s for patients with VL, is a broad-spectrum antibiotic belonging to aminoglycosides, which has a 90% efficacy in patients unsuccessfully treated with antimonials (Table 1). The most dangerous PM-related ADRs are nephrotoxicity and ototoxicity, followed by a curative effect at high doses and allergic reactions. Gastrointestinal ADRs are common and include nausea, vomiting, abdominal pain, and diarrhea (Table 2)[36]. The mechanism of action of PM reflects the pharmacodynamics of aminoglycosides, inhibiting protein synthesis by binding to 16S ribosomal RNA. PM is administered via the IM route at the dosage of 15 mg/kg both alone in Indian patients with VL for up to 21 days or in combination with L-AmB in Indian/East African patients with VL[16]. In murine and dog VL models, PM administered parenterally showed marked leishmanicidal activity[50]. PM is the cheapest anti-leishmaniasis drug, although IM administration makes it less manageable[51]. There is a high risk of developing drug resistance, especially when PM is given as monotherapy and in patients with VL/HIV coinfection[52]. Results from a pharmacovigilance program evaluating over 3000 patients with VL highlighted that sodium stibogluconate and PM combination had a 95% efficacy rate, which was significantly lower in patients with VL/HIV coinfection or in those aged >50 years[53]. No other rates are currently available about PM efficacy in patients with immunocompromised status.

**Table 3. Other pharmacological approaches in visceral leishmaniasis**

| Drug | Reference number | Effects |
|---|---|---|
| Antimonials and interferon gamma | 63 | Improvement of hemoglobin and white blood cell counts, as well as weight gain, decrease in spleen size, and reduction of parasites in splenic aspirates |
| Pentamidine and interferon gamma | 64 | Successful treatment in the case of a 19-year-old patient with VL/HIV coinfection who suffered from fever and pancytopenia |
| Meglumine antimoniate plus interferon gamma | 65 | Improvement of clinical conditions and negative bone marrow cultures in two patients with VL/HIV coinfection |
| N-methylglucamine (antimonial drug) and intramuscular interferon gamma | 66 | Regression of the hepatosplenomegaly in a young patient with VL/HIV coinfection |
| Meglumine antimoniate plus allopurinol | 68 | Clinical and parasitological recovery in five patients with VL/HIV coninfection |
| Ketoconazole | 70 | Improvement of symptoms with no side effects in nine patients with VL |
| Allopurinol and ketoconazole | 71, 72 | Favorable outcomes in two cases, including a renal transplant recipient with VL |
| Astrakurkurone (*In vitro/in vivo* studies) | 73 | Increase of the immune efficiency of host cells stimulating the production of interferon gamma, interleukin-17, and other protective cytokines |

VL: Visceral leishmaniasis, HIV: Human immunodeficiency virus

### Miltefosine

Miltefosine is the only oral drug available for VL treatment, proven to be effective in patients with immunocompromised status (Table 1)[54]. Miltefosine is a phosphocholine analog whose activity is caused by its ability to interfere with cellular metabolic signals, permeability, and lipid composition of cell membranes. According to IDSA guidelines, even if L-AmB is recommended for VL therapy in patients with immunocompromised status, the combination of L-AmB and miltefosine should be considered if relapse or failure occurs; however, when VL is caused by *L. infantum*, the relapse or inefficacy rate can be high in some settings after miltefosine administration[55]. The efficacy and duration of therapy should established in patients with VL/HIV coinfection, and miltefosine has been proposed as secondary prophylaxis in cases reporting high risk of VL relapse, as those with severe impairment of the immunity (i.e., CD4 T-cells <200/mm$^3$)[32]. A study of a Spanish small case series of transplanted patients relapsing after a L-AmB course (six patients) highlighted an initial improvement in all patients and a definitive cure in three of six cases[56]. A 28-day regimen can favor a 90% cure rate in VL-endemic regions, when administered to patients with immunocompromised status. During the first week of treatment, common ADRs are nausea, vomiting, and diarrhea, which can be reduced by taking the drug in divided doses with meals (Table 2). Because of the drug nephro- or hepatotoxicity, therapeutic drug monitoring is recommended once a week. Miltefosine is associated with teratogenicity; therefore, it is contraindicated in pregnant or breastfeeding women, and for women of childbearing age, effective contraception must be ensured during treatment and the subsequent three-month period[57,58]. An open-label, randomized trial conducted in Ethiopian patients with VL/HIV coinfection compared 39 subjects taking L-AmB (total dose, 30 mg/kg) and miltefosine (100 mg/day for 28 days), with 19 patients on L-AmB monotherapy (40 mg/kg). The better efficacy of the combination regimen was demonstrated both at day 29 [81% (95% confidence interval (CI): 67-90%) vs. 70% (95% CI: 45-87%)] and day 58 [88% (95% CI: 79-98%) *vs* 55% (95% CI: 32-78%)], without any major safety concerns related to the study drugs[59]. Regarding the treatment of patients with VL/HIV infection, the Medecins Sans Frontières experience with a combination regimen consisting of L-AmB 30 mg/kg (total dose) and miltefosine for 28 days was demonstrated to be promising, with an initial cure rate of 81%[60]. In an Indian retrospective study of 102 patients with HIV-VL coinfection, a combination regimen of L-AmB 30 mg/kg (divided into six infusions on alternate days) and miltefosine for 14 days lead to the all-cause mortality cumulative incidence of 11.7%, 14.5%, and 16.6% and relapse rates of 2.5%, 6.0%, 13.9%, as assessed after 6-, 12-. and 18-month follow-ups, respectively[61]. In Ethiopia, miltefosine-related ADRs are worse in patients with HIV infection. Sixty-five percent of patients with coinfection experienced vomiting compared with 45% of those affected with VL only. Thirty-nine patients with European coinfection, who had relapsed on previous treatments, were treated with miltefosine, achieving a cure rate of 64%. Even if almost all patients had relapsed again, they were retreated with moderate success, underlying that a prolonged treatment with miltefosine can be safe[62]. A Ethiopian study of patients with coinfection, comparing those receiving antimonials with those receiving miltefosine, showed that miltefosine treatment reported higher therapeutic failure (18% *vs.* 2%) and relapse (25% *vs.*11%) rates after a six-month follow-up period but was associated with lower mortality (6% vs 12%)[23]. The half-life of miltefosine is about seven days, so the risk of inducing drug resistance, especially in relapsing coinfection, should be evaluated[63,64]. Miltefosine use in patients with coinfection should be prolonged until parasite clearance is achieved. In India, where there is an elimination program based on large-scale miltefosine distribution, it is crucial to control the HIV status[65]. Current data suggest that miltefosine resistance can be reported in some settings and that relapse can occur in particular settings in patients with immunocompromised status. Further comparative analysis should support its wider use in immunocompromised cases[66].

### Other Pharmacological Approaches

Some evidence demonstrates the efficacy of the combined regimen of antimonials and interferon gamma in the treatment of patients with VL. Fourteen patients receiving this drug combination reported an improvement of hemoglobin and white blood cell count; weight gain, a decrease in spleen size, and reduction of parasites in splenic aspirates were also observed[67]. Based on case reports, interferon gamma may increase the efficacy of conventional therapy for VL. An 19-year-old former drug abuser with HIV infection also developed VL caused by *L. infantum*; he experienced fever and pancytopenia and reached recovery with interferon gamma/meglumine antimoniate therapy. The same therapy was effective in two of three cases showing relapse after antimonial therapy. In the third case showing relapse, antimonial-related proteinuria and renal failure appeared; therefore, therapy was stopped, and subsequent relapses were successfully treated with pentamidine and interferon gamma[68]. In the other three patients with advanced acquired immunodeficiency syndrome and disseminated leishmaniasis, treatment with meglumine antimoniate plus interferon gamma rapidly improved the patients' clinical conditions, and in two of the three patients, bone marrow cultures were negative. Therapy with interferon gamma was well tolerated, but the effectiveness of preventing relapses remained unclear[69]. Combined therapy with N-methylglucamine (antimonial drug) and IM interferon

gamma was also effective in regressing the hepatosplenomegaly of another young patient with VL-HIV coinfection[70]. The resistance to antimonial drugs can be very frequent; therefore, the use of combined therapy was previously considered a part of the treatment of Indian patients with VL receiving antimonials. Moreover, sodium stibogluconate used in combination with PM or interferon gamma has provided unexpectedly discouraging results, in favor of the combination of AmB and miltefosine, especially in patients with VL-HIV coinfection[71]. Treatment with meglumine antimoniate plus allopurinol was used in patients with VL/HIV coinfection: six patients received treatment for three weeks and five patients for four weeks; 1/6 and 4/5 achieved clinical and parasitological recovery, respectively, and only one patient developed a severe maculopapular rash[72]. Allopurinol plus meglumine antimoniate therapy was effective in four of six patients with VL, who had previously failed to respond satisfactorily to sodium stibogluconate[73]. Nine patients with VL, who failed to respond to sodium stibogluconate or pentamidine, were treated with ketoconazole 600 mg/day for four weeks, which improved their symptoms with no side effects[74]. A case report described stibogluconate-related pancreatitis in a renal transplant recipient treated for VL. Subsequently, the patient received a combination of allopurinol and ketoconazole and had a favorable outcome[75]. In a similar case, in which the patient was found to be intolerant to meglumine antimoniate, the oral administration of ketoconazole (200 mg/12 h) and allopurinol (300 mg/day) for 30 days led to the complete absence of *Leishmania* from the bone marrow aspirate[76]. *In vitro* and *in vivo* investigations demonstrated that astrakurkurone, a triterpene isolated from the Indian mushroom *Astraeus hygrometricus*, increased the immune efficiency of host cells, stimulating the production of interferon gamma, interleukin-17, and other protective cytokines, finally reducing the parasite burden[77]. The aforementioned pharmacological approaches are presented in Table 3.

## Conclusion

The diagnosis of VL can be very insidious in patients with immunocompromised status due to impaired immunity and nonspecific symptoms, and treatment can be aggravated by a high incidence of side effects because of patients' low tolerance. As reported in other cases, repositioning of drugs developed for the treatment of other diseases has been the main strategy to investigate drugs for VL treatment[78]. Several drugs have been tried to verify their effectiveness in this clinical setting; however, only a few of these drugs are available; thus, more studies should be conducted[79]. L-AmB has shown the best risk-benefit ratio, but its high cost and IV route for drug administration makes its use unaffordable for many highly endemic countries. Miltefosine is very manageable, thanks to its oral administration, but we must consider its toxicity and the possibility of resistance. Combination therapies can likely break down drug-resistant VLs.

### Ethics

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: P.P., Concept: C.S., T.A., G.F., O.P., A.F., V.C., P.P., Design: C.S., T.A., G.F., O.P., A.F., V.C., P.P., Data Collection or Processing: C.S., G.S., Analysis or Interpretation: C.S., G.S., V.C., P.P., Literature Search: C.S., G.S., V.C., P.P., Writing: C.S., T.A., G.F., O.P., A.F., V.C., P.P.

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