

# Review of the current treatments for leishmaniasis

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**Abstract:** Leishmaniasis are vector-borne zoonotic diseases that are prevalent in tropical and subtropical areas in the world, with two million new cases occurring yearly. Visceral and tegumentary forms of leishmaniasis are known. The latter form may present as localized cutaneous or mucosal forms, disseminated, diffuse forms, or leishmaniasis recidiva cutis. Visceral leishmaniasis is caused by parasites of the species *Leishmania (Leishmania) donovani* and *L. (L.) infantum*, and tegumentary leishmaniasis is caused by 15 other species, with distinct distributions in the Old and New World. The varied clinical manifestations, the multitude of *Leishmania* species, and the increasing incidence of HIV coinfection make the diagnosis and treatment of leishmaniasis complex. Since there are no solid data relating clinical manifestations, treatment outcomes and *Leishmania* species the decision regarding the best therapeutic option is almost entirely based on clinical manifestations. Because most of the literature is focused on leishmaniasis in the Old World, in this review we present data on the treatment of New World leishmaniasis in more detail. Ranked therapeutic options, clinical trials, and also observations, even with a restricted number of subjects, on treatment outcome of visceral and different forms of tegumentary leishmaniasis, are presented. Treatment for leishmaniasis in HIV-coinfected patients is addressed as well. Some of these data strongly suggest that the differences in the outcome of the treatment are related to the *Leishmania* species. Therefore, although it is not possible at most points of care to identify the species causing the infection – a process that requires a well equipped laboratory – the infecting species should be identified whenever possible. More recent approaches, such as the use of immunomodulators and immunotherapy, and the lines for development of new candidate drugs are mentioned.

**Keywords:** tegumentary, visceral, therapy, HIV

Leishmaniasis are vector-borne zoonotic diseases that are caused by various species of protozoa of the genus *Leishmania*. These pathogens are transmitted by phlebotomine sandflies and infect humans that are exposed to ecosystems where the vectors and reservoirs, either peridomestic or sylvatic, coexist. Anthroponotic cycles have been documented for some species of *Leishmania* and for defined geographical areas such as that of *Leishmania (Leishmania) donovani* in the Indian subcontinent and *L. (L.) major* in Afghanistan. Leishmaniasis are prevalent in tropical and subtropical areas, with two million new cases occurring yearly.<sup>1-3</sup>

Visceral and tegumentary forms of leishmaniasis are known. Visceral leishmaniasis (VL) is caused by *L. (L.) donovani* in the Indian subcontinent and East Africa and by *L. (L.) infantum* in other parts of Asia, Europe, Africa and the New World (where it was formerly referred to as *L. (L.) chagasi*). Tegumentary leishmaniasis (TL) is caused by

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approximately 15 species of parasites: *L. (L.) major*, *L. (L.) tropica*, *L. (L.) aethiopica* and sometimes *L. (L.) infantum* in the Old World and *L. (Viannia) braziliensis*, *L. (L.) amazonensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, *L. (L.) mexicana*, *L. (L.) pifanoi*, *L. (L.) venezuelensis*, *L. (V.) peruviana*, *L. (V.) shawi*, and *L. (V.) lainsoni* in the New World.<sup>3,4</sup> Among species causing TL, different species of subgenus *Viannia* and *L. (L.) amazonensis* (subgenus *Leishmania*) are found from Mexico to Argentina, and the largest variety is present in Brazil, mainly in the Amazon region. *L. (L.) mexicana* is present in Mexico and other Central American countries.

Patients with active VL present with fever, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia, and severe weight loss. The manifestations of TL are varied and are classified as localized cutaneous or mucosal forms, disseminated, diffuse forms, or leishmaniasis recidiva cutis;<sup>5</sup> some of these forms are related to particular species (Table 1). The localized cutaneous form is the initial lesion in most cases, and the progression to other forms depends on the species of *Leishmania* involved and on the host response.<sup>5</sup>

The varied clinical manifestations, the multitude of *Leishmania* species, and the increasing incidence of HIV coinfection make the diagnosis and treatment of leishmaniasis complex. The fact that there are no solid data relating

clinical manifestations, treatment outcomes and *Leishmania* species the decision regarding the best therapeutic option is still based almost entirely on clinical manifestations. Although it is not possible at most points of care to identify the species causing the infection – a process that requires a well equipped laboratory – the infecting species should be identified whenever possible, because differences in treatment outcomes have been reported for localized cutaneous leishmaniasis (CL) caused by *L. (V.) braziliensis* and *L. (V.) guyanensis*.<sup>6–8</sup>

Because most of the literature is focused on leishmaniasis in the Old World, herein we present data on the treatment of New World leishmaniasis in more detail.

## Compounds in current use for the treatment of leishmaniasis

### Pentavalent antimonials

Over the past 70 years, the first-choice drugs for the treatment of leishmaniasis have been pentavalent antimony compounds, which are available in two formulations, methylglucamine antimoniate and sodium stibogluconate.<sup>9</sup> The mechanism of action of pentavalent antimonials is still not well understood, but the drugs inhibit the activity of the glycolytic and oxidative pathways of fatty acids in amastigotes.<sup>10</sup> The most frequent side effects of pentavalent antimonials are arthralgia, myalgia, anorexia, headache, fever, vomiting, and dizziness. These drugs are toxic to the heart, kidneys, liver, and pancreas, and this toxicity represents an important limitation in the use of these drugs by pregnant women, the elderly, and individuals with cardiac disease, renal disease, or liver alterations.<sup>5</sup>

### Amphotericin B

Amphotericin B, a polyenic antibiotic with leishmanicidal activity, acts both on promastigotes and amastigotes and targets ergosterol in the surface membrane of the parasite, leading to increased permeability and the influx of ions.<sup>11</sup> There are four formulations of amphotericin B for clinical use: deoxycholate amphotericin B, liposomal amphotericin B, amphotericin colloidal dispersion, and amphotericin B lipid complex.<sup>5,10</sup> Deoxycholate amphotericin B causes more severe adverse effects that include nausea, vomiting, fever, hypokalemia, renal failure, anemia, and heart problems. The cardiotoxicity, nephrotoxicity, and hypokalemia induced by this drug formulation and its intravenous delivery restrict its use to the hospital environment.<sup>5,12</sup> Liposomal amphotericin B is more expensive; however, it reaches higher peak plasma levels, exhibits a shorter circulating half-life, and

**Table 1** Clinical manifestations of leishmaniasis and related *Leishmania* species

Clinical manifestation	<i>Leishmania</i> species	Geographical area
Localized cutaneous leishmaniasis	<i>L. (L.) tropica</i>	Old World
	<i>L. (L.) major</i>	Old World
	<i>L. (L.) aethiopica</i>	Old World
Disseminated cutaneous leishmaniasis	<i>L. (L.) amazonensis</i>	New World
	of subgenus <i>Viannia</i>	New World
Diffuse cutaneous leishmaniasis	<i>L. (V.) braziliensis</i>	New World
	<i>L. (L.) amazonensis</i>	New World
Leishmaniasis recidivacutis	<i>L. (L.) mexicana</i>	New World
	<i>L. (L.) amazonensis</i>	New World
	<i>L. (L.) aethiopica</i>	Old World
	<i>L. (L.) tropica</i>	Old World
Mucosal leishmaniasis	<i>L. (V.) braziliensis</i>	New World
	<i>L. (V.) panamensis</i>	New World
	<i>L. (V.) guyanensis</i>	New World
	<i>L. (L.) amazonensis</i>	New World
	<i>L. (L.) major</i>	Old World
Visceral leishmaniasis	<i>Leishmania (L.) donovani</i>	Old World, except Europe
	<i>Leishmania (L.) infantum</i>	Europe, Africa, and New World

reaches higher concentrations in the liver and spleen, with much less toxicity than conventional amphotericin B. The lipid component drives the drug into the intracellular milieu, favoring the interaction with ergosterol of the parasite over host cholesterol.<sup>13</sup>

## Pentamidine

Pentamidine is a dibenzamidine that interferes with the synthesis of *Leishmania* DNA acting on the kinetoplast and on the mitochondrial membrane, leading to the death of the parasite. The primary adverse effects are hypotension, myalgia, abscess at the injection site, hypoglycemia, and diabetes mellitus.<sup>5,8,10</sup>

## Miltefosine

Initially developed for the treatment of cancer, miltefosine inhibits phospholipid and sterol biosynthesis and both in vitro and in vivo *Leishmania*. The limitation for its use is its toxicity to the gastrointestinal, hepatic, and renal systems. It is also teratogenic, which restricts its use in pregnant women.<sup>5,8</sup>

## Paromomycin

Paromomycin is a broad spectrum aminoglycoside antibiotic that was found to have leishmanicidal activity in the 1960s. The main side effects are ototoxicity and local pain upon injection.<sup>8,10</sup> The drug supposedly affects plasma membrane fluidity, interferes with ribosomes and mitochondrial membrane potential, inhibiting respiration.<sup>14</sup>

## Imidazoles/triazoles (ketoconazole, fluconazole, itraconazole)

These antifungal drugs include two distinct classes of compounds: imidazoles (eg, ketoconazole) and triazoles (eg, fluconazole and itraconazole). These two classes of compounds share the same antifungal spectrum and the same mechanism of action, but the metabolism of triazoles is slower. In addition, triazoles interfere less with sterol synthesis in humans and are thus less toxic than imidazoles. A great advantage of the azoles used in leishmaniasis is their oral use and lower toxicity relative to pentavalent antimonials.<sup>15</sup>

## Treatment of leishmaniasis

There are few drugs available for the treatment of leishmaniasis as listed in the Table 2.

## VL

VL is caused by two distinct species of *Leishmania*. Concerning clinical manifestations, only *L. (L.) donovani* infection can evolve into post-kalazar dermal leishmaniasis

(PKDL), which is characterized by the appearance of cutaneous lesions containing parasites in the period after treatment of VL.<sup>16</sup>

The drug used to treat active VL is chosen based on risk factors, patient characteristics, geographical area, and *Leishmania* species.

Pentavalent antimonials (sodium stibogluconate or meglumine antimoniate) are the first-line drugs used to treat VL.<sup>17</sup> In the New World, mainly in Brazil, the efficacy of these drugs is higher than 90%,<sup>18</sup> whereas treatment failure is approximately 60% in Bihar, India, and in Nepal.<sup>19,20</sup> When treatment failure occurs or when there are restrictions, alternative drugs are used.

The second-choice drugs are the different formulations of amphotericin B, which have been shown to be effective against different species of *Leishmania* from different geographical areas, exhibiting high efficacy and low toxicity.<sup>19,21</sup> In the Indian subcontinent and Europe, liposomal amphotericin B has been used as a first-line drug due to the resistance to antimonials in some areas;<sup>20</sup> liposomal amphotericin B is used in the United States of America because it is the only treatment approved by the Food and Drug Administration. Recently a single-dose treatment with liposomal amphotericin B was tried in India, with 95% cure.<sup>22</sup> In the New World, mainly in Brazil, amphotericin B has been used successfully to treat VL in particular situations, primarily in older patients, children, transplant recipients, and patients with comorbidities such as diabetes and HIV infection.<sup>18</sup>

Miltefosine, another alternative drug, is used to treat VL in the Indian subcontinent,<sup>23,24</sup> where it exhibits high efficacy; it is used primarily to treat moderate VL. In contrast, in the New World, miltefosine was shown to be less effective than a pentavalent antimonial in a clinical trial that had to be discontinued (personal communication). Systemic paromomycin is a new option to treat VL in the Indian subcontinent and exhibits high efficacy.<sup>25,26</sup> In East Africa, the efficacy of paromomycin was found to be lower, and therefore it is recommended that a higher dose be used or that the drug be used in combination with a pentavalent antimonial.<sup>27</sup> There has been no trial with paromomycin in the New World to date.

The evaluation of clinical recovery during and after treatment is based on the remission of fever, the reduction of splenomegaly and hepatomegaly, and the improvement of hematological disturbances.<sup>3</sup> There is no consensus regarding the parasitological or immunological methods that should be used to evaluate treatment success, but such methods are used in some centers to determine whether patients have been cured. The cure rate is typically 90%–95%, and the

**Table 2** Medicines with doses used to treat tegumentary and visceral leishmaniases<sup>a</sup>

	Pentavalent antimonials	Amphotericin B deoxycholate	Liposomal amphotericin B	Pentamidine isethionate	Miltefosine
Localized cutaneous leishmaniasis	10–20 mg/Sb <sup>+5</sup> /kg/day (iv or im) 10–20 days	1 mg/kg/day (iv) Total dose: 1.0–1.5 g		4 mg/kg/day (im) Maximum dose: 2 g	2.5 mg/kg (oral) 28 days to treat <i>L. mexicana</i>
Disseminated cutaneous leishmaniasis	20 mg/Sb <sup>+5</sup> /kg/day (iv or im) 28 days	1 mg/kg/day (iv) Total dose: 1.0–1.5 g		4 mg/kg/day (im) Maximum dose: 2 g	
Diffuse cutaneous leishmaniasis	20 mg/Sb <sup>+5</sup> /kg/day (iv or im) 28 days			Not used	Not used
Leishmaniasis recidiva cutis	15–20 mg Sb <sup>+5</sup> /kg (iv or im) per day for 28 days <sup>b</sup>				
Mucosa leishmaniasis	20 mg/Sb <sup>+5</sup> /kg/day (iv or im) 30 days	1 mg/kg/day (iv) Total dose: 2.0–2.5 g	2–3 mg/kg/day (iv) Total dose: 40–60 mg/kg	Not used	2.5 mg/kg (oral) 28 days <sup>c</sup>
Visceral leishmaniasis	20 mg/Sb <sup>+5</sup> /kg/day (iv or im) for 28 days <sup>d</sup>	0.75–1.00 mg/kg/day (iv) 15–20 doses	3–4 mg/kg/day (iv) Total dose: 15–24 mg/kg	Not used	2.5 mg/kg (oral) 28 days <sup>e</sup>

**Notes:** <sup>a</sup>Doses and time of treatment were based on WHO recommendation from 2010; <sup>b</sup>in case of no response to the usual dose of Sb<sup>+5</sup>, Sb<sup>+5</sup> plus allopurinol 20 mg/kg for 30 days is indicated when *L. tropica* is the agent; <sup>c</sup>only in Bolivia; <sup>d</sup>except Bihar (Indian subcontinent); <sup>e</sup>only in the Indian subcontinent.

**Abbreviations:** Sb<sup>+5</sup>, pentavalent antimonial; iv, intravenous; im, intramuscular.

endpoint of the follow-up period to assess relapse is 6 months after treatment.<sup>3</sup> For relapses, the second-choice drugs and combinations of different drugs are used. Another complication is the appearance of PKDL in 5%–10% of patients after the apparent cure of VL caused by *L. (L.) donovani*;<sup>16</sup> the appearance of PKDL is not considered a relapse, and PKDL is treated with the same drug as used to treat VL but for an extended duration.<sup>3</sup>

The recommendation of HIV testing in patients with recent VL diagnosis should be emphasized because the treatment response in coinfecting patients is poorer than in noncoinfecting patients.

## CL of the Old World

In the Old World, CL caused by *L. (L.) major* has been treated with local paromomycin/methylbenzethonium chloride ointment, intralesional antimonials, and cryotherapy or thermotherapy when the lesion is small and not disfiguring or disabling, and when the patient is not immunosuppressed. When the disease is caused by the species *L. (L.) tropica*, *L. (L.) aethiopica*, or *L. (L.) infantum*, the preferred local treatment is intralesional antimonials alone or thermotherapy or cryotherapy alone. When systemic treatment is required, the choices are fluconazole or pentavalent antimonials plus pentoxifylline.<sup>3,28</sup> For the treatment of leishmaniasis recidiva cutis caused by *L. (L.) tropica*, the use of pentavalent antimonials plus oral allopurinol is recommended. For the treatment of diffuse CL caused by *L. (L.) aethiopica*, pentavalent antimonials plus intramuscular paromomycin are used.<sup>3,28</sup>

## CL of the New World

Local treatment in clinical trials using paromomycin in different formulations have shown varied results, from a 64% cure rate in Colombia<sup>29</sup> to an 88.6% cure rate in a double-blind study in Guatemala; the difference in the cure rates may be related to the *Leishmania* species that are prevalent in each area. Currently, the topical treatment of CL in the New World is not recommended, except in cases of infection with *L. (L.) mexicana* or in areas where the severe forms of the disease are very rare, as in Venezuela and Colombia.<sup>30</sup>

The use of pentavalent antimonials resulted in a 5% therapeutic failure rate among cases of CL caused by *L. (V.) braziliensis*.<sup>29</sup> It was observed that 7%, 16%, and 39% of patients were refractory to treatment in Brazil, Bolivia, and Colombia, respectively; the infecting species were not identified in these studies.<sup>31,32</sup> A randomized study that compared drugs showed that 40% of patients with CL caused by *L. (V.) braziliensis* who were treated exclusively with an antimonial required more than two or three courses of treatment to achieve a cure.<sup>33,34</sup> Although spontaneous remission has been reported in the literature, it is infrequent among cases of CL caused by *L. (V.) braziliensis*, and there is a risk that the patient will develop mucosal leishmaniasis (ML) if no treatment is given. Costa et al<sup>35</sup> reported the results of clinical evaluations carried out over a period of 14 years in field clinics in the communities of Três Braços and Corte de Pedra, Bahia, Brazil involving 1416 patients with TL caused predominantly by *L. (V.) braziliensis*. Most of these patients received antimonial treatment, but 16 male patients refused treatment, and six pregnant female



patients were not treated. During the patient follow-up period of 4–12 years, the observed healing time was 6 months for nine patients (40.9%); complete healing after 12 months was observed for 19 patients (86.3%), and no healing after 12 months was observed in three (13.6%) cases.<sup>35</sup>

In some studies, liposomal amphotericin B has been used to treat patients with CL caused by *L. (V.) guyanensis*,<sup>36</sup> *L. (V.) braziliensis*,<sup>37</sup> *L. (L.) infantum*,<sup>38</sup> or *L. (L.) aethiopica*.<sup>39</sup> However, larger studies are needed to assess the effectiveness of amphotericin B for the treatment of CL.<sup>40</sup>

Pentamidine has been used successfully in areas endemic for CL due to *L. (V.) guyanensis* (4 mg/kg on days 1 and 4).<sup>41</sup> The rate of treatment failure depends on when the treatment was started; a 5% failure rate was observed when the treatment was started within the first month of disease, and a 25% failure rate was observed when treatment was started later.<sup>41</sup> In areas where infections are caused by *L. (V.) braziliensis*, *L. (V.) shawi* and *L. (V.) guyanensis*, the use of three intramuscular doses of 4 mg/kg on days 1, 3, and 5 is recommended, not exceeding a maximum dose of 300 mg/day. The effectiveness of this regimen was similar to that of 20-day antimonial treatment, reaching a 70%–75% cure rate; a lower dose and a shorter duration resulted in a 35% cure rate<sup>42</sup> or liposomal amphotericin B.

Miltefosine was used initially in 2005 in Colombia for the treatment of TL.<sup>15</sup> In Bolivia, oral miltefosine (2.5 mg/kg/28 days) was compared with an intramuscular antimonial (20 mg/kg/20 days) to treat TL caused by *L. (V.) braziliensis*,<sup>43</sup> and the cure rates after 6 months were 88% (36/41) and 94% (15/16), respectively. In Colombia, where *L. (V.) panamensis* is common, the same dose of oral miltefosine resulted in a 91% cure rate, similar to the cure rate for antimonials, whereas the cure rate of the placebo group was 38%.<sup>44</sup> In Guatemala, where *L. (V.) braziliensis* and *L. (L.) mexicana* predominate, the cure rate for miltefosine was only 53%, significantly lower than the cure rate for antimonials.<sup>44</sup> Thus, further studies are needed to specifically assess the value of miltefosine in the treatment of TL in the New World and to investigate the activity of miltefosine against different *Leishmania* species.

Regarding azoles, studies in Guatemala (N = 120 patients) and Belize (N = 8) assessed the efficacy of a 28-day regimen of oral 600 mg ketoconazole and found a lower cure rate (30% and 25%, respectively) among patients infected with *L. (V.) braziliensis* compared with the rate among patients infected with *L. (L.) mexicana* (89% and 100%, respectively). Moreover, among patients infected with *L. (V.) panamensis*, ketoconazole seemingly has a performance similar to that

of antimonials.<sup>45</sup> However, the interpretation of these data should take into account the fact that CL caused by *L. (L.) mexicana* and *L. (V.) panamensis* has a high spontaneous cure rate.<sup>45</sup>

Drug combinations that include pentavalent antimonials have been recommended in an attempt to increase the efficacy, reduce the dose, and decrease the prevalences of side effects and therapeutic failure.

## ML

The frequency of ML varies according to the *Leishmania* species involved and to the geographical region. Andean countries have one of the highest frequencies of ML, with an average incidence of 7.1%.<sup>30</sup> Only systemic drugs are used for the treatment of ML. The cure rates are variable and depend on the geographical area, the *Leishmania* species involved, and the drug used for treatment.<sup>46,47</sup>

Pentavalent antimonials are the most used drugs to treat ML around the world. Different doses have been evaluated, and doses other than the recommended dose are occasionally used; however, the decision to use a different dose must be based on structured studies within the same area and with the same *Leishmania* species.<sup>48,49</sup> The cure rate after treatment using pentavalent antimonials varies from 30% to 90%.<sup>50</sup>

Because some reports using liposomal amphotericin B formulations for the treatment of ML have shown excellent results, liposomal amphotericin B can be an alternative treatment; however, the optimal doses for the treatment of ML have not been completely defined.<sup>51</sup> The use of pentamidine has been evaluated in Brazil, and healing was observed in nine (90%) of the ten patients who received 2140 mg and were followed up for 7.7 months.<sup>50</sup> Although the results are promising, few studies have been conducted to confirm this drug's effectiveness due to its severe adverse effects and the discontinuity of drugs.

Miltefosine was used to treat ML in Bolivia, showing cure rates of 71% and 74% in patients treated for four<sup>52</sup> and six<sup>53</sup> weeks, respectively. However, the secure rates are lower than that for amphotericin B but similar to that for pentavalent antimonials.

## Criteria of cure and follow up

There is no consensus on the criteria of cure in the literature, and this fact results in some controversial data seen in reported cure rate upon treatment. It would be desirable to have standardized criteria to be used in different studies based on clinical, parasitological parameters and the follow up time. In Brazil only the clinical criteria are considered,

since other parameters are not satisfactory for this purpose. CL is considered cured when total epithelialization of the lesion and absence of any induration at the base of the ulcer are achieved within 3 months of treatment. ML is considered cured when regression of all clinical signs is achieved within 6 months of treatment. When these criteria are not reached, it is considered a relapse.<sup>54</sup>

### Leishmania/HIV coinfection

HIV is present worldwide and is gradually spreading into areas endemic for leishmaniasis, leading to the appearance of *Leishmania*/HIV coinfection. The interaction of these two infections accelerates both disease processes, worsening the prognosis of both.<sup>3,55,56</sup>

More data concerning treatment are available for coinfecting patients with VL, mainly from the Old World. Therefore, more studies of patients with TL are needed because this form is more frequent in the New World, accounting for approximately 63% of coinfecting patients.<sup>57</sup>

For the treatment of VL in HIV-infected patients, the same drugs as used to treat noncoinfecting patients are used. Coinfecting patients more often experience adverse events, treatment failures, and relapses than immunocompetent individuals.<sup>3,55,56</sup> Cardiotoxicity, nephrotoxicity, and pancreatic damage are responsible for interruptions in treatment.<sup>56,58,59</sup>

Varied cure rate has been observed in HIV-coinfecting patients treated with pentavalent antimonials. In Ethiopia cure rate was 58.3%<sup>60</sup> and 58.6%,<sup>61</sup> while in Brazil it reached 68.4% (personal data). When used as rescue treatment upon treatment failure with liposomal amphotericin B presented, the cure rate reaches 83%. However, in this group, high mortality was observed, probably due to the adverse effects of pentavalent antimonials.<sup>59</sup>

Liposomal amphotericin B in different doses has been used to treat VL in HIV-infected patients. When liposomal amphotericin B was used at a total dose of 30 mg/kg, an initial cure rate of 59.8% was observed.<sup>59</sup> In India, using a total dose of 20–24 mg/kg, the cure rate was 74.5%,<sup>62</sup> and in Brazil using the same dose it reached 63% (personal data).

Miltefosine has been used in Ethiopia, and the cure rate was 46% in HIV-coinfecting patients.<sup>61</sup>

Systemic treatment with paromomycin exhibited good efficacy among HIV-positive patients with VL in the Indian subcontinent (94%) and Ethiopia; however, the efficacy of this treatment in Sudan was low. The efficacy and safety of systemic paromomycin are still unknown in other areas.<sup>63</sup>

Pentamidine was previously used for the treatment of VL, but due to resistance in the Indian subcontinent, its use was abandoned.<sup>63</sup> Currently, the use of pentamidine as a prophylactic agent is accepted because it is easy to administer, causes few adverse events, and exhibits minimal interference with antiretroviral therapy.<sup>3</sup> However, clinical trials are still needed to demonstrate the efficacy of pentamidine as a secondary prophylactic agent in HIV-positive patients.

The cure rate in VL patients coinfecting with HIV is always lower than in HIV-negative patients, independent of whether they are treated with pentavalent antimonials or liposomal amphotericin B.

Because it has been reported that the efficacy of liposomal amphotericin B is limited, it has been proposed that higher doses be used to prevent resistance and to achieve a better cure rate;<sup>21</sup> high doses can be used because of the low frequency of adverse events such as nephrotoxicity.<sup>55,64</sup>

Antiretroviral treatment, which promotes increases in the CD4+ T cell count and decreases in the viral load in HIV-positive patients, is suggested to have an anti-*Leishmania* effect.<sup>58</sup> Even when the CD4+ T cell count is restored, secondary prophylaxis for VL is necessary for a long period to prevent relapses in coinfecting patients. The reduction of the incidence of VL, the high survival rate of patients, high relapse rates, and possible immune reconstitution inflammatory syndrome are some impacts of antiretroviral therapy on VL.<sup>3</sup> Further, combining antiretroviral therapy with anti-*Leishmania* drugs seemingly prevents resistance, increases tolerance and efficacy, and reduces the duration and cost of VL treatment.<sup>65</sup>

Among patients with TL, poorer responses to standard treatment and frequent relapses have been reported.<sup>66,67</sup> The cure rate of TL is variable and depends on immune status and the *Leishmania* species that is present. Recently, Guerra et al<sup>68</sup> showed that the poor response to pentavalent antimonial treatment in co-infected patients was related to the high prevalence of *L. (V.) guyanensis* in the Amazon region. In the Old World, poor responses to pentavalent antimonials have been observed among HIV-infected patients with CL caused by *L. (L.) tropica*.<sup>65</sup> Independent of the *Leishmania* species, poor response to treatment is observed among HIV-infected patients, especially among those who are severely immunosuppressed.

### Future of the treatment for leishmaniasis

To improve the treatment, different approaches have been evaluated, which include the use of immunomodulators and immunotherapy. For these approaches, basic information on

the immune response and its progression during the disease course in leishmaniasis patients is important.

During active CL, there is a predominance of CD4<sup>+</sup> T cell response, and upon treatment the production of interferon-gamma increases while that of IL-10 decreases.<sup>69</sup> However, in ML, a high level of tumor necrosis factor (TNF)- $\alpha$  is observed during active lesion, which decreases with therapy.<sup>70</sup> Therefore, cytokines and inflammatory response modulators have been used in combination with other drugs, showing promising results. Pentoxifylline, an inhibitor of TNF- $\alpha$ , and imiquimod, an activator of Toll-like receptor 7 and a mediator of inflammatory cytokine production, have been used in association with antimonials to treat TL showing, respectively, reduction in the time to cure<sup>71,72</sup> or increase of cure rate to 90% in patients refractory to antimonials.<sup>73,74</sup> Association of interferon- $\gamma$  with antimonials is also effective in curing TL patients presenting resistance to antimonials.<sup>75</sup> Topical recombinant human granulocyte-macrophage colony-stimulating factor in combination with antimonials was also shown to reduce the healing time 50%.<sup>76</sup>

As immunotherapy, *Leishmania* antigen, whole promastigote preparations, recombinant *Leishmania* antigens as Leish-111f, alone or in combination with adjuvants such as bacillus Calmette-Guérin (BCG) and monophosphoryl lipid A,<sup>77</sup> have shown promising results.<sup>78</sup> Immunotherapy in association with drugs is an option to preclude toxicity and emergence of resistance related to some drugs. Only in Venezuela is immunotherapy with whole promastigote preparation with BCG as adjuvant in current use to treat CL.<sup>79,80</sup>

The development of new candidate drugs is in progress, following mainly three lines. One focuses on plants as a source of anti-protozoal molecules, the other explores metabolic pathways of the parasite to find the target and to develop synthetic compounds,<sup>81</sup> and the more immediate approach is the repositioning of the medicines already on the market for other purposes. From the latter approach, amphotericin B, miltefosine, and pentoxifylline, for example, have been previously developed, and presently, tamoxifen, a drug used for breast cancer, is being studied.<sup>82</sup>

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## Disclosure

The authors report no conflicts of interest in this work.

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