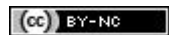


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Treatment of American tegumentary leishmaniasis in special populations: a summary of evidence

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ABSTRACT

We aimed to assess and synthesize the information available in the literature regarding the treatment of American tegumentary leishmaniasis in special populations. We searched MEDLINE (via PubMed), EMBASE, LILACS, SciELO, Scopus, Cochrane Library and mRCT databases to identify clinical trials and observational studies that assessed the pharmacological treatment of the following groups of patients: pregnant women, nursing mothers, children, the elderly, individuals with chronic diseases and individuals with suppressed immune systems. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The available evidence suggests that the treatments of choice for each population or disease entity are as follows: nursing mothers and children (meglumine antimoniate or pentamidine), patients with renal disease (amphotericin B or miltefosine), patients with heart disease (amphotericin B, miltefosine or pentamidine), immunosuppressed patients (liposomal amphotericin), the elderly (meglumine antimoniate), pregnant women (amphotericin B) and patients with liver disease (no evidence available). The quality of evidence is low or very low for all groups. Accurate controlled studies are required to fill in the gaps in evidence for treatment in special populations. Post-marketing surveillance programs could also collect relevant information to guide treatment decision-making.

Keywords: American tegumentary leishmaniasis. Special populations. Treatment. Evidence.

INTRODUCTION

Some patient populations present challenges for the treatment of American tegumentary leishmaniasis (ATL). These populations include pregnant women, nursing mothers, children, the elderly, individuals with chronic diseases and individuals with suppressed immune systems. These individuals are excluded from clinical trials¹ to achieve homogeneous groups. As a result, the available evidence on the effectiveness and safety of treatments in special populations of patients is scarce², which makes clinical decision-making difficult.

The therapeutic options available to treat ATL are limited, and the current evidence for recommendations on the treatment of cutaneous leishmaniasis (CL) is generally weak³⁻⁵. Pentavalent antimonials (SbV) have been the drugs of choice for more than six decades. However, they have high toxicity and are contraindicated in children, pregnant and breastfeeding women and chronically ill patients⁶⁻⁹. Pentamidine isethionate and amphotericin B are the second-line treatments^{7,9,10}. In the last decade, miltefosine was introduced as an oral alternative¹¹

whose effectiveness for treating CL and mucosal leishmaniasis (ML) was shown in clinical trials conducted in Guatemala, Colombia, Bolivia and Brazil¹²⁻¹⁷.

The present study reports results found from a literature review of the treatment of ATL in special populations.

METHODS

Study type: this is a summary of evidence with systematic search, selection and data extraction processes.

Study eligibility criteria: clinical trials and observational studies were considered eligible if they assessed pharmacological treatment using the main drugs used in the treatment of ATL (meglumine antimoniate, amphotericin, pentamidine isethionate and miltefosine) in one of the following patient populations: pregnant women, nursing mothers, children (individuals under 16 years of age), the elderly (individuals over 60 years of age) and individuals with renal disease, heart disease, liver disease or suppressed immune systems (e.g., individuals with human immunodeficiency virus (HIV) infection or individuals receiving therapy with immunosuppressive drugs or bone marrow or solid organ transplantation). For renal, heart and liver disease, we considered the same definition that the included papers employed.

Studies regarding the treatment of diseases other than ATL, such as mycoses, were not considered eligible. However, when there was a lack of specific studies for ATL in special groups, additional studies regarding visceral leishmaniasis (VL) or Old World CL were also assessed.

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LITERATURE SEARCH

In November 2010, a broad search was conducted by one of the authors (JSFS) in MEDLINE (via PubMed), EMBASE, LILACS, SciELO, Scopus, Cochrane Library and mRCT. There was no restriction on language or publication date. The search strategy included the following terms: *leishmaniasis, cutaneous, mucocutaneous, pentamidine, amphotericin B, meglumine antimoniate, miltefosine, adverse effects, new world leishmaniasis, American leishmaniasis, side effects and undesirable effects*. The last search update was performed on July 2013.

Secondary sources of information were also consulted: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and the World Health Organization (WHO)¹⁸⁻²⁰.

Study selection and data extraction: one author selected the studies from the titles and abstracts (JSFS) and another confirmed the data (TFG). The same process was used to extract relevant information regarding anti-leishmanial drugs used in special populations.

Data analysis and critical appraisal: the studies were labeled as laboratory studies, case reports, case series, case-control studies, cohort studies, narrative reviews, systematic reviews or clinical trials and grouped according to the special population of patients studied: pregnant women, nursing mothers, children, the elderly, patients with chronic diseases and patients with suppressed immune systems.

Regarding the drugs used for treatment, the U.S. FDA Pregnancy Category Definitions¹⁸ were used to rate the best pharmacotherapy option for pregnant women. To classify the risk for nursing mothers, we adopted the WHO Breastfeeding and Maternal Medication Recommendations for Drugs²⁰, which consider five categories ranging from *compatible with breastfeeding* to *avoid using*.

After the eligible studies were selected, the evidence presented was rated based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach²¹. No information produced by regulatory agencies was considered for the assessment of the quality of evidence.

RESULTS AND DISCUSSION

Ninety-seven references were found regarding therapeutic options for ATL treatment in pregnant women, nursing mothers, children, the elderly, and patients with renal disease, heart disease, liver disease or suppressed immune systems (**Figure 1**). Most of the included studies were case reports (**Table 1**). The special group with the highest number of publications was patients with suppressed immune systems. No description was found for anti-leishmaniasis therapy in nursing mothers. For children, six clinical trials were available. Although a clinical trial was found for the renal disease group, it was not considered for the treatment quality assessment because its purpose was the prevention of nephrotoxicity. The quality of the evidence was very low for most groups, including children (**Table 2**).

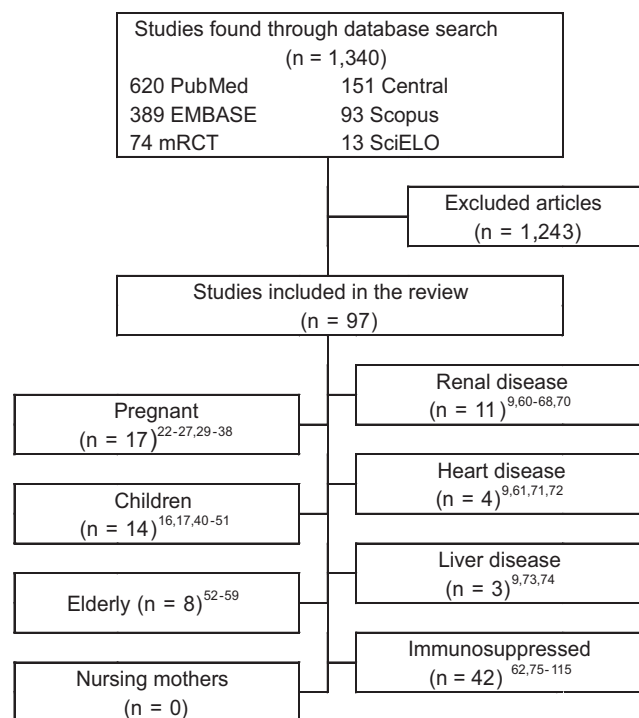


FIGURE 1 - Search results and selection of articles per special group. Note: The search on LILACS did not retrieve any results. References⁶¹ and ⁶² were included for more than one group, what makes the total of included studies less than the sum of all studies by group. Numbers in superscript represent the references list.

Pregnant women: only amphotericin B is acceptable for use during pregnancy according to the FDA¹⁸ (**Table 3**). Although the FDA pregnancy category provides guidance regarding a drug's potential fetal risks, limitations such as a lack of a specific toxic dose or predisposing pregnancy trimester complicate its application²². Amphotericin B can cross the placenta and reach low concentrations in the amniotic fluid²³, but its safety in pregnant women was established in the treatment of systemic mycoses¹⁸. No studies were found assessing the effectiveness of amphotericin B in ATL treatment. In pregnant women with VL, amphotericin is preferred over other drugs²⁴. Moreover, there were no adverse effects on the fetus or abortions when it was used for VL during the first or second trimester^{25,26}.

Information regarding meglumine antimoniate safety in pregnancy is scarce²⁷. Pentavalent antimonials are considered a category C drug by the FDA¹⁸ (**Table 3**). Experimental studies in pregnant rats showed an increase in fetal skeletal malformations, particularly in the atlas bone²⁸. In addition, this drug may be toxic to the embryo even in the absence of signs of maternal toxicity²⁹.

In humans, the evidence for meglumine antimonite treatment in pregnant women with ATL is limited. There are two case reports of patients using the drug in the first trimester. The drug was discontinued as soon as pregnancy was identified without harm to fetus, pregnant mother or labor³⁰. Other studies report the treatment of 70 VL pregnant women with SbV. Among

TABLE 1 - Studies classified according to type by each special group reported in this review.

Study type	Special populations								Total
	pregnant women	nursing mother	children	the elderly	renal disease	heart disease	liver disease	immuno suppressed	
Laboratory study*	4 ^{27,29,37}	NA	1 ⁴⁰	NA	1 ⁶⁷	NA	2 ^{73,74}	1 ⁷⁷	9
Case reports	3 ^{24,30,31}	NA	4 ^{44,46-48}	1 ⁵⁹	3 ^{61,62,68}	2 ^{61,72}	NA	30 ^{62,75,76,78,79,82-91,93-98,103,107-114}	42
Case series†	2 ^{25,26}	NA	1 ⁴⁵	3 ^{54,57,58}	-	NA	NA	3 ^{81,99,102}	9
Case-control study	NA	NA	NA	NA	NA	NA	NA	1 ⁸⁰	1
Cohort study	2 ^{32,38}	NA	1 ⁴³	4 ^{52,53,55,56}	3 ^{60,63,64}	1 ⁷¹	NA	-	11
Narrative review‡	6 ^{22,23,33-36}	NA	1 ⁵¹	NA	1 ⁷⁰	NA	NA	6 ^{92,94,100,101,106,115}	14
Systematic review	NA	NA	-	NA	2 ^{9,65}	1 ⁹	1 ⁹	1 ¹⁰⁷	5
Clinical trial	NA	NA	6 ^{16,17,41,42,49,50}	NA	1 ^{66§}	NA	NA	1 ¹⁰⁴	8
Total	17	0	14	8	11	4	3	42	-

*Laboratory experimental studies; †includes retrospective studies of series of patients treated (medical records); ‡ narrative review on the main therapeutic options available; § clinical trial on preventing amphotericin nephrotoxicity; || one study¹⁰⁷ presented a case report and a systematic review in the same manuscript; NA: not available. Numbers in superscript represent the references list.

TABLE 2 - Quality of evidence for American tegumentary leishmaniasis therapy in special groups (Adapted from GRADE).

Drug	Special groups							
	pregnant woman	nursing mother	children	the elderly	renal disease	heart disease	liver disease	immune suppressed
Meglumine antimoniate	very low	NA	low	very low	NA	very low	very low	very low
Pentamidine	NA	NA	low	NA	NA	NA	NA	very low
Amphotericin B	very low	NA	very low	NA	very low	NA	NA	very low
Liposomal amphotericin	very low	NA	very low	NA	very low	NA	NA	very low
Miltefosine	very low	NA	low	NA	very low	NA	very low	very low

NA: not available; GRADE: Grading of Recommendations, Assessment, Development and Evaluations.

these 70 women, there were 16 cases of abortion in the first or second trimester^{26,31,32}.

Pentamidine isethionate should be avoided during pregnancy. The FDA category risk for this drug is C (Table 3) because the drug's manufacturer did not conduct animal reproductive studies. In studies conducted after the drug was marketed, pentamidine was teratogenic but not embryocidal when administered to animals. Pentamidine may cross the human placenta¹⁸.

Miltefosine has exhibited teratogenicity and should therefore not be administered to pregnant women³³⁻³⁵. Studies in rats and rabbits have demonstrated embryotoxicity, fetotoxicity and teratogenicity^{28,29,36}. Compulsory contraception is required for

women of childbearing age who intend to use miltefosine³⁷. Furthermore, as a precaution, conception should be delayed for 2³⁶ to 4 months³⁸ after treatment ends. There is no rating for the use of miltefosine during pregnancy because it is not registered by the FDA (Table 3).

Nursing mothers: according to the WHO, meglumine antimoniate and pentamidine isethionate are the only two drugs for ATL treatment that are compatible with breastfeeding²⁰ (Table 3). Data regarding the use of amphotericin B by breastfeeding women are lacking²².

The SbV concentration in breast milk is low (3.5mg Sb/ml), with little effect on the newborn³⁹. The excretion of amphotericin B, pentamidine isethionate and miltefosine in breast milk is

TABLE 3 - Safety recommendations for drugs used for American tegumentary leishmaniasis treatment in pregnant women and nursing mothers.

Drug	Pregnancy*	Breastfeeding†
Meglumine antimoniate	C	CB
Amphotericin B	B	NA
Liposomal amphotericin	B	NA
Pentamidine	C	CB
Miltefosine	NA‡	NA

*Index of drug toxicity criteria adopted by the FDA, United States of America¹⁸⁻²⁰; †Index of Breastfeeding and Maternal Medication Recommendations for Drugs by World Health Organization¹⁸⁻²⁰; ‡ Although miltefosine is not registered by the FDA, its use is contraindicated in pregnancy; B: remote possibility of fetal harm; animal studies showed no risk to the fetus; there are no studies in humans; C: possible harm to the fetus; insufficient controlled studies in humans and animals; CB: compatible with breastfeeding; FDA: Food and Drug Administration. NA: not available.

unknown. Therefore, these drugs are not recommended in nursing mothers. No data are available regarding the risk to the child¹⁸ (Table 3).

Children: mMost studies found included children between 2 and 12 years of age. According to the Brazilian health authorities, meglumine antimoniate is the drug of choice to treat pediatric patients³⁹. The maximum daily dose of SbV for children under 12 years of age must not exceed 121.5mg (7.5ml), and treatment of children under 18 months is not recommended³⁹. However, CL treatment with meglumine antimoniate is less effective in children than in adults^{40,42}. The lower efficacy may result from the pathogenicity of the parasite or the particular immune response of this age group^{40,42}. Meglumine antimoniate for the treatment of CL seems to reduce blood cell counts and liver enzymes more frequently in children than in adults and appears to significantly increase serum amylase and lipase levels⁴³. A sickle cell crisis has been reported as an adverse effect of CL treatment with meglumine antimoniate in a 6-year-old child in Colombia⁴⁴.

Intra-lesional meglumine antimoniate seems to be an alternative for children with CL. An infusion of the maximum dose of 10ml at intervals of 7 to 15 days proved to be more effective and better tolerated than conventional intramuscular treatment in this age group in Brazil⁴⁵.

Scarce data are available for ATL treatment with amphotericin B in children. We found three case reports of children infected by *Leishmania (Viannia) braziliensis* treated with amphotericin deoxycholate whose CL lesions were cured without adverse effects^{46,47}. In contrast, VL treatment with liposomal amphotericin showed no difference in efficacy or safety between children and adults¹⁸. In a double-blind study with pediatric patients (16 years of age or younger), liposomal amphotericin presented a lower incidence of hypokalemia, chills, vomiting and hypertension than amphotericin deoxycholate¹⁸.

Pentamidine treatment for CL is considered to represent an unlabeled use by the FDA¹⁸. The CDC recommended dose for children is 2 to 3mg/kg IM or IV on alternate days for 4-7 doses¹⁹. In Brazil, a 14 year-old girl with CL was cured after pentamidine treatment⁴⁸, and a recent randomized controlled trial (RCT) including children with CL showed similar efficacy of pentamidine and meglumine in the treatment of ATL⁴⁹ caused by *Leishmania (Viannia) guyanensis*.

Oral administration and low toxicity favor the use of miltefosine in this age group⁵⁰. There were two RCTs including children 2 to 12 years of age with CL in Brazil^{16,17} and one in Colombia⁵⁰. The cure rate of miltefosine was non-inferior compared to meglumine antimoniate^{16,17,50}. However, miltefosine was less effective for children infected by *Leishmania guyanensis* in Brazil¹⁷, possibly because of lower plasma concentrations of miltefosine in children⁵¹. The most frequently reported adverse event was vomiting (12/28 children; 43%)¹⁷.

The elderly: in the treatment of ATL, the patient's age should be considered, as most adverse reactions occur in individuals over 50 years of age⁵². Pentavalent antimonials are the most widely adopted drugs for CL treatment in elderly patients. However, there are no pharmacokinetics studies in this group. The incidence of CL in the population over 65 years of age is increasing significantly⁵³. American tegumentary leishmaniasis patients between 60 and 92 years of age were studied in Brazil. Of the 44 patients, 36 (82%) had CL, and eight (18%) had mucocutaneous leishmaniasis (MCL). Low-dose meglumine antimoniate was administered three times a day (5mg/kg/day) with complete resolution in 33 (75%) cases. However, treatment was discontinued in nine (21%) subjects because of moderate to severe adverse effects, such as hypoglycemia, anemia, pancreatitis, increased transaminase levels, thrombocytopenia and renal failure⁵⁴. Adverse events such as renal tubular dysfunction and hematological, heart and liver abnormalities are common causes of treatment interruption in this age group. Advanced age is one of the risk factors for tinnitus, which affects 5% of elderly patients using meglumine antimoniate⁵³. Electrocardiogram abnormalities associated with meglumine antimoniate are more frequent in the elderly. Angiotensin-converting enzyme inhibitors may have a cardioprotective effect in older patients using meglumine antimoniate⁵⁵. Secondary infection was also observed more frequently in patients older than 45 years of age ($p < 0.04$) subjected to meglumine antimoniate intralesional treatment for CL⁵⁶. This is an effective and less toxic alternative treatment for CL patients with contraindications to systemic therapy⁵⁷. Cutaneous leishmaniasis patients younger than 65 years of age without co-morbidities can be safely and effectively treated in specialist centers with parenteral SbV without hospital admission⁵⁸.

No studies were found for ATL treatment with amphotericin in the elderly. However, it was not necessary to change the standard dose of liposomal amphotericin in elderly patients treated for other diseases. Careful monitoring is recommended¹⁸.

There were also no studies for ATL treatment with pentamidine in elderly patients. A 64-year-old woman who developed severe hypokalemia under meglumine antimoniate treatment for Old World ML was successfully treated with miltefosine⁵⁹.

Patients with kidney disease: pentavalent antimonials are contraindicated for ATL treatment in patients with severe renal impairment. Renal evaluation studies are rare in ATL. Urinary concentration and acidification defects were found in a significant number of patients treated with SbV⁶⁰. These drugs should therefore be used with caution in patients with any renal dysfunction. A patient with previous renal problems presenting with MCL was submitted to a course of prednisolone combined with the SbV treatment and had a good response to treatment. Adjuvant glucocorticoid therapy provided symptomatic relief⁶¹.

Liposomal amphotericin may represent a safe, efficient and less toxic alternative therapy for ATL; it was safely used in a patient with kidney failure and diabetes mellitus who was on dialysis. Healing of CL lesions was achieved with a total dose of 600mg⁶² even though amphotericin B is associated with dose-dependent nephrotoxicity, particularly when the daily dose is greater than 35mg. Risk factors that predispose patients to this condition are as follows: body weight over 90kg, concomitant cyclosporine or aminoglycoside usage, chronic renal failure (CRF)⁶³, male sex, advanced age and jaundice⁶⁴. Patients with more than two risk factors for nephrotoxicity are potential candidates for alternative therapy⁶³. Amphotericin B delivered as a locally prepared lipid emulsion or in liposomes may reduce nephrotoxicity⁶⁵.

A randomized controlled trial conducted in Peru with MCL patients⁶⁶ showed that hydration with oral hyperosmolar solution was as effective as parenteral hydration to prevent glomerular injury caused by amphotericin B. Laboratory studies indicate that hypokalemia predisposes patients to tubular damage from amphotericin B⁶⁷.

Pentamidine is contraindicated in patients with CRF. This drug has slow excretion from the body and can accumulate in the kidneys and liver. Thus, pentamidine must be used with caution in patients with renal dysfunction¹⁸.

Miltefosine may be an alternative for ATL treatment in patients with renal impairment. There is a case report of CL in an elderly patient with CRF who was treated with 1.8mg/kg/day of miltefosine for 28 days. The patient's skin lesions healed and no adverse events were reported⁶⁸. However, 1% of miltefosine patients may develop nephrotoxicity⁶⁹. Mild to moderate increases in creatinine are an adverse effect related to miltefosine⁹. Therefore, renal function should be monitored.

A recent literature review on renal involvement in VL suggests that SbV, amphotericin B, pentamidine, miltefosine, paromomycin and sitamaquine may be associated with a high risk of renal toxicity⁷⁰.

Patients with heart disease: meglumine antimoniate is contraindicated in patients with heart disease³⁹, and it is associated with arrhythmias and conduction disorders in adults with no previous heart disease⁷¹. Electrocardiographic QTc interval prolongations are an adverse effect related to SbV^{9,61}. However, these changes are usually reversible after drug discontinuation. A case of pericarditis was reported in a CL patient treated with systemic meglumine antimoniate⁷².

Amphotericin B is also associated with the occurrence of arrhythmias. Therefore, its use for ATL treatment in cardiac patients requires close monitoring. Rapid infusions should be avoided to prevent arrhythmias and local irritation¹⁸.

Pentamidine should be used with caution in patients with preexisting heart disease. Hypotension, hypertension and arrhythmia, including ventricular tachycardia, have been reported. Pentamidine is known to prolong the QT interval and subsequently increases the risk of occurrence of torsade de pointes¹⁸.

We could not find a description in the medical literature of cardiac adverse events during ATL treatment with miltefosine^{13,14,16,17}.

Patients with liver disease: there are no studies of ATL treatment with meglumine antimoniate in patients with liver impairment. Meglumine antimoniate is contraindicated in patients with severe liver disease. Mild to moderate increases in liver and pancreatic enzyme levels are adverse effects related to SbV⁹. Case reports of hepatitis arising from its use have been described. Therefore, another drug is recommended for treatment¹⁸.

The pharmacokinetics of liposomal amphotericin were not studied in patients with chronic liver disease⁷³.

Pentamidine should be used with caution in patients with liver dysfunction¹⁸.

The clearance of miltefosine is performed by hepatocyte phospholipases⁷⁴, and 1% of patients using it may develop hepatotoxicity⁶⁹. Mild to moderate increases in aminotransferase levels were adverse effects related to miltefosine⁹. Therefore, laboratory monitoring of liver function is recommended.

Patients with suppressed immune systems: ATL infection is emerging as a result of immunosuppression, and HIV is the most common cause^{62,75-88}. Bone marrow or solid organ transplantation⁸⁹⁻⁹⁵ and therapy with immunosuppressive or biologic drugs⁹⁶⁻⁹⁸ also have been associated with the appearance of ATL. In immunosuppressed patients, CL is characterized by atypical cutaneous lesions and persistent negativity of diagnostic tests⁹¹.

Human immunodeficiency virus/acquired immunodeficiency syndrome: the association between ATL and HIV-AIDS has increasingly been described in many regions of the world⁹⁹ together with immune reconstitution inflammatory syndrome presentation^{82,84,85,100}.

The evidence for the treatment of co-infection with HIV and LC is still very limited¹⁰¹. Generally, systemic therapy is used to prevent the spread of the parasite. The same approach used for immunocompetent individuals is applied with weekly monitoring³⁹. Recurrences are frequent^{80,86} and fatal cases have been reported⁸⁶. A series of 15 patients with ATL/HIV-AIDS association in Brazil was recently published, where only seven patients were successfully treated at the first attempt⁹⁹. Leishmaniasis was the first opportunistic infection in 60% of patients in another case series of 23 HIV patients recently investigated in Brazil. The cluster of differentiation antigen 4 (CD4)+ T-cell count was below 200 cells/mm in 80% of cases and did not increase after clinical remission despite antiretroviral therapy. The first drug chosen to treat the cases was SbV, but the therapeutic regimen was altered to amphotericin B in 12 of 17 cases because of side effects. Relapses were reported in 56% of the patients¹⁰².

An HIV-positive patient with MCL caused by *L. braziliensis* was treated successfully with a short course of meglumine antimoniate⁷⁵. However, SbV showed no therapeutic response in four LM co-infected patients. Cardiotoxicity occurred in three cases. Pentamidine and amphotericin were more effective⁷⁸. Pentamidine was used to treat HIV-infected patients with CL caused by *L. guyanensis* in a case-control study in French Guiana. HIV patients had a higher rate of recurrence or reinfection and a lower rate of recovery after pentamidine treatment⁸⁰.

In Bolivia, amphotericin deoxycholate was used for 80 days to treat HIV-infected patients with CL caused by *L. braziliensis* without success⁸⁷. However, liposomal amphotericin showed a good response in two cases of co-infected MCL and HIV patients who had not responded to meglumine antimoniate^{76,103}. In addition, liposomal amphotericin was also used successfully in co-infected CL and HIV patients with a 1,500mg dose⁶².

Patients co-infected with HIV and ATL have been treated with miltefosine with initial success, but then relapsed^{104,105}. However, Old World CL patients with HIV were cured with miltefosine after treatment failure with conventional amphotericin B, liposomal amphotericin and sodium stibogluconate^{81,83}. An experimental study in immunosuppressed rats suggests that miltefosine may be useful in both the acute and maintenance phases⁷⁷.

Other types of immune system suppression - There were no studies of ATL treatment in patients with other types of immune system suppression. However, treatment of patients with VL and Old World CL has been reported. In transplant recipients,

CL and ML are rare and usually there is a time interval between transplantation and disease manifestation¹⁰⁶. Reviews of organ transplant recipients with leishmaniasis show that the majority of patients have undergone renal transplantation, and most cases are identified as visceral-type disease^{93,107-109}.

Patients presenting LV after organ transplantation treated with SbV presented with amylase and lipase elevation in addition to pancreatitis¹¹⁰. In contrast, a CL case treated with intralesional injections of meglumine antimonate was reported after 20 months of infliximab treatment for ankylosing spondylitis (uveitis and arthritis). Infliximab was discontinued, and local treatment led to rapid improvement¹¹¹.

An 83-year-old patient with myelodysplastic syndrome was treated successfully with liposomal amphotericin for CL caused by *Leishmania major* without adverse effects¹¹². Renal transplantation patients presenting with VL also had a good response to liposomal amphotericin^{110,113}. However, toxicity occurred in patients with LV after heart transplantation, and treatment needed to be interrupted¹¹⁴.

Use of pentamidine or miltefosine has not been reported in other populations of immunosuppressed patients¹¹⁵.

In conclusion, a summary of the more appropriate ATL therapeutic options for each special population reviewed in this paper is shown in **Table 4**. A common finding in all groups is the low or very low quality of evidence. There is a need for controlled studies of higher quality, ideally randomized controlled trials. Post-marketing surveillance programs could play a role in filling the existing gaps in knowledge.

TABLE 4 - Summary of the proper American tegumentary leishmaniasis treatment options reviewed for each special population.

Special populations	Drug of choice	Evidence level
Pregnant women	amphotericin B	very low
Nursing mother	NA†	NA
Children	meglumine antimoniate or miltefosine for <i>Leishmania braziliensis</i> ; meglumine antimoniate or pentamidine for <i>Leishmania guyanensis</i>	low
The elderly	meglumine antimoniate (low dose or intralesional injections)*	very low
Renal disease	amphotericin B or miltefosine	very low
Heart disease	amphotericin B or pentamidine or miltefosine (used with caution) ¹⁸⁻²⁰	very low
Liver disease	NA	NA
Immunosuppressed patients	liposomal amphotericin	very low

NA: not available. †: according to the World Health Organization, the drugs for American tegumentary leishmaniasis treatment that are compatible with breastfeeding are meglumine antimoniate and pentamidine isethionate²⁰. This evidence however, was not found in clinical trials and observational studies, the study design that was eligible for inclusion in this review. *To avoid toxicity or when systemic therapy is contraindicated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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