

## Short Communication

# Cost-effectiveness analysis of diagnostic-therapeutic strategies for visceral leishmaniasis in Brazil

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### Abstract

**Introduction:** Visceral leishmaniasis (VL) is fatal if not diagnosed and treated. This study aimed to estimate the cost-effectiveness of diagnostic-therapeutic alternatives for VL in Brazil. **Methods:** A decision model estimated the life expectancy and costs of six diagnostic-therapeutic strategies. **Results:** IT LEISH + liposomal amphotericin B emerged the best option, presenting lower costs and higher effectiveness. DAT-LPC + liposomal amphotericin B showed an incremental cost-effectiveness ratio of US\$ 326.31 per life year. **Conclusions:** These findings indicate the feasibility of incorporating DAT and designating liposomal amphotericin B as the first-line drug for VL in Brazil.

**Keywords:** Visceral leishmaniasis. Cost-effectiveness. Diagnosis. Therapy.

Visceral leishmaniasis (VL) is a neglected tropical disease (NTD) occurring in five continents<sup>1</sup>. The disease is a severe and expensive public health problem in Brazil<sup>2</sup>, causing more deaths than dengue or malaria<sup>3</sup>. According to the Brazilian Ministry of Health (MH), 4,511 new cases of VL were reported in 2017, and 323 of these patients died<sup>4</sup>.

Currently, the MH offers in its reference laboratory system an indirect fluorescence antibody test (IFAT; Biomanguinhos/Oswaldo Cruz Foundation) and the OnSite™ *Leishmania* IgG/IgM Combo test (CTK Biotech, USA) for serological diagnosis of VL. IFAT is Brazil's most widely used test and requires a complex laboratory infrastructure and trained technicians; however, it exhibits poor performance, with sensitivity and specificity ranging from 88 to 92% and 83 to 88%, respectively<sup>5-6</sup>.

OnSite™ *Leishmania* IgG/IgM Combo test (CTK Biotech, USA) and IT LEISH are rapid tests registered by the National Agency of Sanitary Surveillance of Brazil (Agência Nacional de Vigilância Sanitária – ANVISA), which are standardized for use with serum and blood<sup>7</sup>. However, no data was available on the performance of OnSite™ *Leishmania* IgG/IgM Combo test for diagnosing VL in Brazil. The sensitivity and specificity of IT LEISH ranges from 92 to 93% and 92 to 98%, respectively<sup>6,8</sup>. The IT LEISH was replaced by the OnSite™ *Leishmania* IgG/IgM Combo test in the Brazilian public health system in 2017 and in 2018 a validation study was performed using a serum panel<sup>9</sup>.

An economic analysis recently conducted in Brazil involving five diagnostic tests showed that a direct agglutination test (DAT) was the most cost-effectiveness diagnostic option for VL<sup>10</sup>. In the present study, the DAT evaluated was an in-house test produced at the Clinical Research Laboratory of the René Rachou Institute. DAT is easily performed and interpreted; it requires simple infrastructure and exhibits high performance, with sensitivity and specificity estimated at 96.2 to 99.5%<sup>11</sup>.

The MH recommends the following drugs for the treatment of VL: N-methylglucamine antimoniate, amphotericin B deoxycholate, and liposomal amphotericin B. The first

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is recommended as the first-line treatment. Liposomal amphotericin B is indicated for patients with severe disease, those presenting comorbidities or immunodeficiencies, pregnant women, and those with renal or cardiac toxicity caused by antimoniate derivatives<sup>12</sup>. In a randomized clinical trial recently conducted in Brazil, Romero et al.<sup>13</sup> reported an effectiveness of 77.5% and 87.2% for N-methylglucamine antimoniate and liposomal amphotericin B, respectively.

Although each diagnostic test and treatment regimen has specific characteristics in terms of effectiveness and cost, no complete economic evaluation of these associated technologies has been performed in Brazil. Therefore, the present study aimed to estimate the cost-effectiveness of diagnostic-therapeutic alternatives for VL in Brazil.

This cost-effectiveness analysis of diagnostic tests and therapeutic regimens for VL used in Brazil was carried out by modeling, using data available in the literature. The study was conducted following all recommendations of Methodological Guidelines for Studies of Economic Evaluation of Health Technologies of the MH<sup>14</sup>.

A decision model was constructed using the software TreeAge Pro 2015 to estimate the life expectancy and cumulative costs of six diagnostic-therapeutic strategies for VL from the perspective of the Unified Health System (Sistema Único de Saúde; SUS).

The decision tree generated began with a suspected case of VL seeking assistance at a referral center. A patient from an endemic area for VL was identified as the clinical suspect, presenting fever associated with at least one of the following signs or symptoms: splenomegaly, hepatomegaly, anemia, leukopenia, or thrombocytopenia. **Figure 1** shows the basic structure of the generated decision tree.

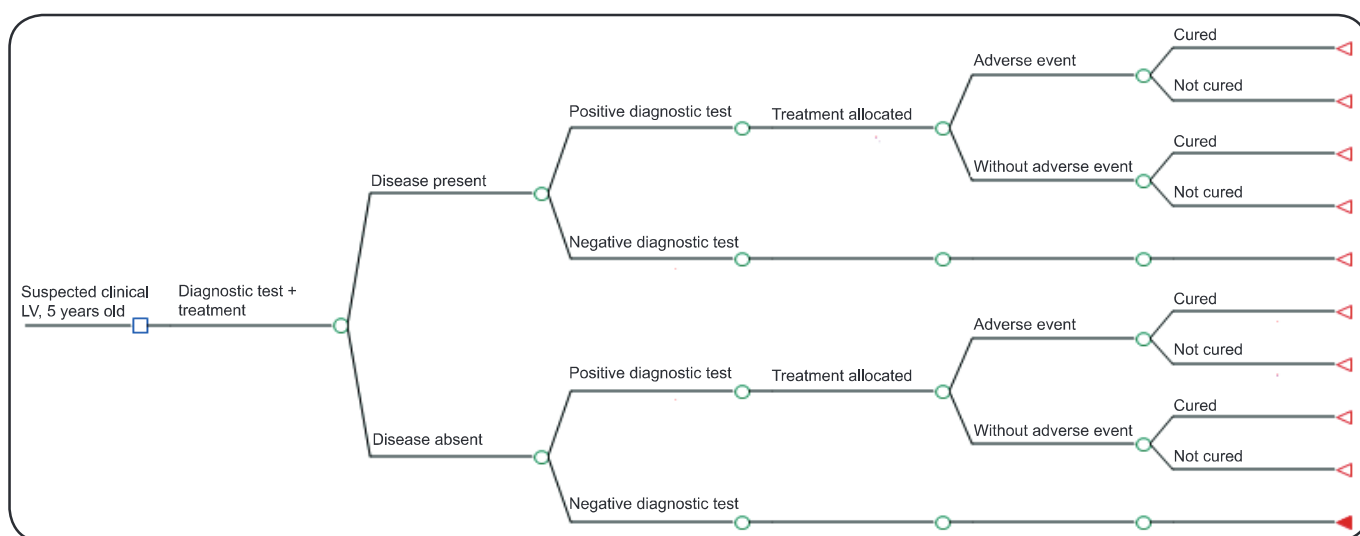
The following six diagnostic-therapeutic strategies were compared: 1) IT LEISH performed using the digital capillary

blood + intravenous treatment with N-methylglucamine antimoniate (20 mg per kg/day for 30 days); 2) IT LEISH performed using the digital capillary blood + treatment with liposomal amphotericin B administered at the hospital (3 mg per kg/day for 7 days); 3) IFAT + intravenous treatment with N-methylglucamine antimoniate (20 mg per kg/day for 30 days); 4) IFAT + treatment with liposomal amphotericin B administered at the hospital (3 mg per kg/day for 7 days); 5) DAT-LPC + intravenous treatment with N-methylglucamine antimoniate (20 mg per kg/day for 30 days); and 6) DAT-LPC + treatment with liposomal amphotericin B administered at the hospital (3 mg per kg/day for 7 days).

Considering the results of Romero et al.<sup>13</sup>, the age of 5 years was defined as the intervention age. Life expectancy for individuals who reached this age was obtained from the general mortality table for the Brazilian population in 2015. The analyses considered crude and adjusted values, applying a discount rate of 5% per year in life expectancy estimates, as recommended by the MH<sup>14</sup>.

The analysis included the following assumptions: the analytic horizon of the decision tree is six months and it is modeled for the entire life; the life expectancy of patients diagnosed with VL and successfully treated is equal to that of the general population; the VL mortality rate in untreated patients is 100%; liposomal amphotericin B will continue to be available at a reduced price for developing countries; patients diagnosed with VL are treated with a single therapeutic regimen; and all costs included in the analysis are incurred at the present time.

Direct costs of diagnostic tests and therapeutic strategies were estimated through micro-costing. Data on the direct cost, sensitivity, and specificity of the diagnostic tests were obtained from Machado de Assis et al.<sup>10</sup>, while those on the direct costs of therapeutic strategies were obtained from Machado de Assis et al.<sup>15</sup>. The rates of cures and adverse events were extracted from Romero et al.<sup>13</sup>.



**FIGURE 1:** Basic structure of the decision tree developed to compare diagnostic-therapeutic strategies for human visceral leishmaniasis.

The cost of adverse events was estimated at US\$ 44.32, which refers to the hospitalization package of 2 to 10 days reimbursed by SUS for the treatment of a patient with a protozoal disease. Considering that all costs included in the analysis were incurred at the present time, there was no cost adjustment for inflation or rebate rates. All probabilities and costs used in the decision model have been summarized in Table 1.

The initial cost–effectiveness analysis was performed only for Diagnostic–Therapeutic Strategies 1 to 4. Specifically, it compared only strategies that included diagnostic tests and therapeutic strategies currently recommended by the Brazilian MH. Subsequently, a new analysis was performed including Strategy 5 and 6.

The incremental cost–effectiveness ratio (ICER), a measure of efficiency, was calculated by dividing the incremental cost of a given diagnostic–therapeutic strategy by its incremental effectiveness (i.e., year of life gained) compared with the previous strategies.

Sensitivity analyses were conducted considering alternative parameters of performance and costs of diagnostic tests and therapeutic regimens. The variation in “costs of diagnostic tests and therapeutic regimens” considered  $\pm 25\%$  of the value estimated by Machado de Assis et al.<sup>10</sup>. The variation in the “performance of the tests” considered the upper and lower bounds of the 95% confidence interval previously determined by Machado de Assis et al.<sup>15</sup>. The “cure rate” and “adverse events” considered the upper and lower bounds of the 95% confidence interval previously determined by Romero et al.<sup>13</sup> (Table 1).

The cost–effectiveness analysis showed that IT LEISH + liposomal amphotericin B (strategy 2) absolutely dominated the other strategies, presenting lower cost and higher effectiveness. In the analysis that included all six strategies, IT LEISH + liposomal amphotericin B remained the best option in terms of cost–effectiveness, with DAT-LPC + liposomal amphotericin B (strategy 6) showing an ICER of US\$ 326.31 per life year gained without a discount rate of 5% per year, and US\$ 12.42 when applying a discount rate of 5% per year (Table 2).

The variation in the performance of the tests showed that, when the sensitivity of DAT was  $\leq 94.0\%$ , IT LEISH + liposomal amphotericin B (Strategy 2) was the only cost–effectiveness option. Variations in cure and adverse events rates, and cost of diagnostic tests did not influence the result of the sensitivity analysis. DAT-LPC + liposomal amphotericin B (Strategy 6) remained cost–effectiveness, even when the cost of DAT-LPC increased to US\$ 49.92, which is 10 times the estimated direct cost.

In the sensitivity analysis evaluating the cost of treatment and considering the six strategies, IT LEISH + N-methylglucamine antimoniate (Strategy 1) was cost–effectiveness when the cost of liposomal amphotericin B was  $\geq$  US\$ 701.02. IT LEISH + liposomal amphotericin B (Strategy 2) presented an ICER of US\$ 99.61 and US\$ 3.79 per year of life gained, without and with a discount rate of 5% per year, respectively, and DAT+ liposomal amphotericin B (strategy 6) presented an ICER of US\$ 347.09 and US\$ 13.22 per year of life gained, without and with a discount rate of 5% per year, respectively.

However, when the cost of N-methylglucamine antimoniate was  $\leq$  US\$ 627.56, IT LEISH + N-methylglucamine antimoniate

TABLE 1: Probabilities and costs related to the diagnostic tests and therapeutic strategies included in the model.

Details	Probability	Diagnostic tests			Therapeutics strategies		Reference
		IT LEISH	IFAT <sup>a</sup>	DAT-LPC <sup>b</sup>	N-methylglucamine antimoniate	Liposomal amphotericin B	
Prior probability of visceral leishmaniasis %	0.67	-	-	-	-	-	Machado de Assis et al. <sup>10</sup>
Sensitivity %	-	94.0	88.3	99.0	-	-	Machado de Assis et al. <sup>10</sup>
Confidence interval 95%	-	90.1–96.3	84.0–92.0	94.0–100	-	-	Machado de Assis et al. <sup>10</sup>
Specificity %	-	100	83.0	98.0	-	-	Machado de Assis et al. <sup>10</sup>
Confidence interval 95%	-	97–100	75.0–88.2	93.0–100	-	-	Machado de Assis et al. <sup>10</sup>
Cure rate %	-	-	-	-	77.5	87.2	Romero et al. <sup>13</sup>
Confidence interval 95%	-	-	-	-	68.6–84.9	79.4–92.8	Romero et al. <sup>13</sup>
Adverse events %	-	-	-	-	75.0	65.0	Romero et al. <sup>13</sup>
Confidence interval 95%	-	-	-	-	65.6–82.5	55.4–74.0	Romero et al. <sup>13</sup>
Direct cost US\$	-	6.57	11.39	4.92	669.40	659.79	Machado de Assis et al. <sup>10,15</sup>
Range $\pm 25\%$	-	4.92–8.21	8.54–14.23	3.69–6.15	502.05–836.74	494.85–824.73	Machado de Assis et al. <sup>10,15</sup>

<sup>a</sup>Indirect Fluorescence antibody test; <sup>b</sup>Direct agglutination test prepared in the Clinical Research Laboratory of the René Rachou Institute, Oswaldo Cruz Foundation, Brazil.

**TABLE 2:** Cost, effectiveness, and incremental cost–effectiveness of diagnostic–therapeutic strategies for visceral leishmaniasis in Brazil.

Diagnostic–therapeutic strategies	Cost (US\$)	Effectiveness with a discount of 5% year	Effectiveness without a discount of 5% year	ICER <sup>a</sup> with a discount of 5% year (US\$)	ICER <sup>a</sup> without a discount of 5% year (US\$)
<b>Analysis 1</b>					
IT LEISH + liposomal amphotericin B	440.25	2.40	62.95	-	-
IT LEISH + N-methylglucamine antimoniate	449.09	2.22	58.43	Dominated	Dominated
IFAT <sup>b</sup> + liposomal amphotericin B	456.02	2.30	60.44	Dominated	Dominated
IFAT <sup>b</sup> + N-methylglucamine antimoniate	465.08	2.14	56.21	Dominated	Dominated
<b>Analysis 2</b>					
IT LEISH + liposomal amphotericin B	440.25	2.40	62.95	-	-
IT LEISH + N-methylglucamine antimoniate	449.09	2.22	58.43	Dominated	Dominated
IFAT <sup>b</sup> + liposomal amphotericin B	456.02	2.30	60.44	Dominated	Dominated
IFAT <sup>b</sup> + N-methylglucamine antimoniate	465.08	2.14	56.21	Dominated	Dominated
DAT-LPC <sup>c</sup> + liposomal amphotericin B	466.21	2.48	65.04	326.31	12.42
DAT-LPC <sup>c</sup> + N-methylglucamine antimoniate	472.55	2.30	60.28	Dominated	Dominated

<sup>a</sup>Incremental cost–effectiveness ratio; <sup>b</sup>Indirect Fluorescence antibody test; <sup>c</sup>Direct agglutination test prepared in the Clinical Research Laboratory of the René Rachou Institute, Oswaldo Cruz Foundation, Brazil.

(Strategy 1) was cost–effectiveness. IT LEISH + liposomal amphotericin B (Strategy 2) presented an ICER of US\$ 102.10 and US\$ 3.88 per year of life gained, without and with a discount rate of 5% per year, respectively, and DAT + liposomal amphotericin B (Strategy 6) presented an ICER of US\$ 636.31 and US\$ 12.42 per year of life gained, without and with a discount rate of 5% per year, respectively. In summary, all strategies including IFAT or N-methylglucamine antimoniate were not economically viable.

World Health Organization (WHO) recommended that rapid tests and DAT as the most appropriate serological tests for VL diagnosis. IT LEISH became available for the Brazilian public health system in 2015, with the aim of decentralizing the VL diagnosis. The test is easy to perform and provides a visual interpretation of the reactions and results within 30 minutes. Another advantage of IT LEISH is the possibility of performing the test at the bedside using capillary blood.

In 2017, the OnSite™ *Leishmania* IgG/IgM Combo test (CTK Biotech, USA) became available in Brazil, despite of the absence of studies evaluating its effectiveness for diagnosing VL based on *L. infantum*. Considering this change in the diagnostic scenario, it would be useful to carry out a new economic assessment once the performance of the new test is established.

DAT is the serological method of choice in several countries, and implementation of this test in Brazilian local laboratories might represent progress in operability, performance, and access<sup>11</sup>. As DAT-LPC is not yet commercially available, for the present analysis, its cost was estimated based on the findings of a technical and economic feasibility study (unpublished data).

IFAT was confirmed as a non-economically feasible test. This result strengthens the recommendation of other authors indicating the substitution of IFAT by DAT in Brazil<sup>6,11</sup>. Although IFAT is a serological test that is used most widely in Brazil for VL diagnosis, of the total number of reported VL cases in 2017 (4511), only 37% (1667) were confirmed by IFAT, which may

be associated to its poor performance and also to a deficient structure of access to the test in Brazil<sup>4</sup>.

Regarding VL treatment, liposomal amphotericin B was the more cost–effectiveness. This result complements the findings of Romero et al.<sup>132</sup>, which revealed low toxicity and acceptable efficacy rates for liposomal amphotericin B, indicating it as a more advantageous alternative for first-line treatment of VL in Brazil. Alonso et al.<sup>16</sup> also reported similar results in a cost–effectiveness study on diagnostic–therapeutic strategies for VL in Morocco. In the present study, the combination of rapid test + liposomal amphotericin B treatment was the most cost-effective option.

Liposomal amphotericin B is a very expensive drug; its production is concentrated in the United States and its patent is in an expiration phase. Considering the market price in Brazil, treatment cost for an adult VL patient is US\$ 11,239.36, as determined by the Drug Regulation Board (Câmara de Regulação de Medicamentos; CMED) of ANVISA. To promote access to more effective and safe treatments for neglected populations in developing countries, an agreement between the WHO and the pharmaceutical company Gilead Sciences was established in January 2010, ensuring a significant reduction in the price of liposomal amphotericin B. Machado de Assis et al.<sup>15</sup> estimated the cost of VL treatment with liposomal amphotericin B to be US\$ 659.79, as based on the value of the drug negotiated by the WHO.

This study is the first to address the cost–effectiveness of different diagnostic–therapeutic strategies for VL in Brazil. The findings might be useful in guiding public policies and for the rational planning of health program spending. The results highlight the need to re-evaluate the diagnostic tests and therapeutic options currently recommended in Brazil, corroborating the feasibility of use of DAT and liposomal amphotericin B as the first-line approach for VL in Brazil.

Conflict of Interest: The authors declare that there is no conflict of interest.

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