

Visceral leishmaniasis in a Brazilian endemic area: an overview of occurrence, HIV coinfection and lethality

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ABSTRACT

The Brazilian municipality of *Rondonópolis*, Mato Grosso State, represents an important visceral leishmaniasis (VL) endemic area. This study described epidemiological and clinical aspects of the occurrence, VL/HIV coinfection and lethality related to VL in *Rondonópolis*. Data from autochthonous cases reported between 2011 and 2016 were obtained from official information systems. During this period, 81 autochthonous cases were reported, with decreasing incidence through 2016. Contrastingly, the lethality rate was 8.6% overall, but varied widely, reaching a peak (20%) in 2016. Almost 10% of patients had VL/HIV coinfection. The occurrence of VL prevailed among men (56.8%), brown-skinned (49.4%), urban residents (92.6%), aged 0-4 years (33.3%). Housewives or retired (29.6%) were the most affected occupational groups. Lower age was the main difference among the total VL cases and those who were coinfecting or died. Clinically, fever, weakness and splenomegaly were more frequent among all VL cases and VL/HIV coinfecting individuals. Bacterial infections ($p=0.001$) and bleeding ($p<0.001$) were associated with death due to VL. Pentavalent antimonial and liposomal amphotericin B were the first choices for treatment among all VL cases (71.6%) and those who died (71.4%), respectively. VL/HIV patients were equally treated with both drugs. These findings may support control measures and demonstrate the need for further investigations.

KEYWORDS: Visceral leishmaniasis. Epidemiology. Lethality. HIV. Coinfection.

INTRODUCTION

Visceral leishmaniasis (VL), or kala-azar, is a vector-borne zoonotic disease that represents a challenge for Brazilian public health, mainly due to its recent expansion to medium and large urban areas¹, in addition to high rates of associated mortality². Brazil is among the six countries that comprise 90% of VL cases worldwide³, where approximately 3,500 new cases are reported annually, with an average lethality of 8.1%^{2,4}.

Death outcomes in VL are often related to delayed diagnosis⁵, drug toxicity⁶, and inadequate management of patients with signs of unfavorable disease evolution^{7,8}. In this regard, age <5 and >40-50 years, jaundice, thrombocytopenia, bleeding, diarrhea, severe neutropenia, dyspnea, and bacterial infections were recently revised as stronger prognostic factors for death due to VL⁷. In addition, human immunodeficiency virus (HIV) co-infections deserve attention as a factor commonly associated with VL lethality⁹. In Brazil, the number of individuals with VL/HIV coinfections has been increasing and this population presents three times higher lethality than patients without VL/HIV coinfections¹⁰.

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Therefore, it is important to evaluate the occurrence of VL in endemic areas, as well as the characteristics among VL/HIV coinfecting patients and those who evolved to death due to VL. These contributions are crucial for the development, optimization and conduction of strategies to control the disease and achieve better management of patients⁹⁻¹¹.

In the past decade, the Brazilian municipality of *Rondonópolis* has emerged as an important VL endemic area. According to Werneck¹², from 2001 to 2012, *Rondonópolis* was among the ten cities responsible for 15.0% of VL cases reported in Brazil. Despite this great importance, the area lacks studies regarding the disease occurrence. The only report described the spatial distributions of human cases, reservoirs and vectors¹³. Thus, the present study aimed to describe epidemiological and clinical aspects of the occurrence, VL/HIV coinfection and lethality of VL in the municipality of *Rondonópolis* between 2011 and 2016.

MATERIALS AND METHODS

Design and study area

This is a retrospective sectional and descriptive study carried out in *Rondonópolis* (16°28'15"S and 54°38'08"W), an agricultural and industrial reference center located in the South of Mato Grosso State in Central-Western Brazil. Although the State includes regions of Amazonia and *Pantanal*, *Rondonópolis* is located in the *Cerrado* biome. The municipality has an estimated population of 222,316 inhabitants and a total area of 4,159.12 km², of which 129.2 km² are located in the urban area¹⁴. The actions of the National VL Surveillance and Control Program are currently carried out by public health authorities and are focused on humans, reservoirs and vectors¹⁵.

Data collection

Data were obtained by the individual analysis of VL notification/investigation forms and death certificates available from the Brazilian Notifiable Diseases Information and Mortality Information Systems, respectively, which are coordinated by the Epidemiological Surveillance Sector of the Municipal Health Department of *Rondonópolis*. All autochthonous cases reported and confirmed in the municipality from resident individuals, between 2011 and 2016, were included. Relapses or cases reported in duplicate were excluded. In order to estimate the annual incidence of VL in *Rondonópolis*, the annual population estimates

from the Brazilian Institute of Geography and Statistics were used¹⁴.

Data analysis

Data were tabulated and the patients were divided into three groups for the characterization of epidemiological and clinical features: total VL cases (all autochthonous VL cases reported in *Rondonópolis*), VL/HIV cases (all autochthonous cases of VL/HIV coinfection) and deaths due to VL (all deaths related to VL). It is important to note that the last two groups are contained in the first. Descriptive statistics were used for the analysis in MicrosoftTM Office Excel 2010 (Microsoft Corp., Santa Rosa, CA, USA) and Epi InfoTM version 7.2 (CDC, Atlanta, GA, USA). Fisher's exact tests were performed to verify associations between groups and clinical manifestations and to compare lethality among patients with VL/HIV coinfections and those without. Both analyses were conducted using STATA/SE 11.0 (StataCorp LP, College Station, TX, USA). Differences with a *p*-value < 0.05 were considered statistically significant.

RESULTS

During the evaluated period, 117 VL cases were reported in *Rondonópolis*, of which 81 (69.2%) were new and autochthonous. The highest incidence of VL was observed in 2011 (12.1/100,000 inhabitants), followed by 2012 (7.9/100,000 inhabitants) and a sharp decline until 2016 (4.6/100,000 inhabitants). In contrast, the overall lethality rate was 8.6%, but varied widely over the years, reaching a peak of 20.0% in 2016 (Figure 1).

Table 1 summarizes the epidemiological aspects for all autochthonous VL cases reported in *Rondonópolis* (n = 81),

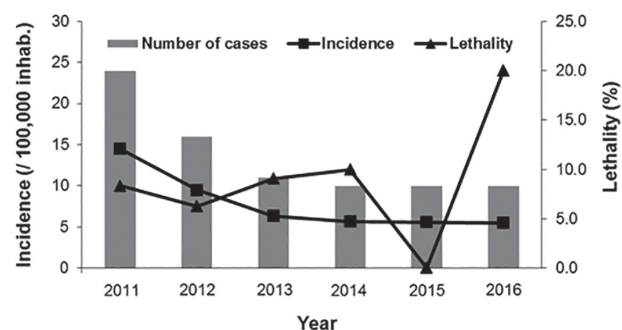


Figure 1 – Number of cases, incidence and lethality rate due to visceral leishmaniasis in the municipality of *Rondonópolis*, Mato Grosso State, Brazil, between 2011 and 2016. To calculate the incidence, the following population estimates provided by the Brazilian Institute of Geography and Statistics were used: 2011/198,949 inhabitants; 2012/202,309 inhabitants; 2013/208,019 inhabitants; 2014/211,718 inhabitants; 2015/215,320; 2016/218,899 inhabitants

Table 1 – Epidemiological characteristics related to the total cases of visceral leishmaniasis (total VL cases), VL/HIV coinfection (VL/HIV cases) and lethality due to VL (deaths due to VL) reported in the municipality of *Rondonópolis*, Mato Grosso State, Brazil, between 2011 and 2016

Variable	Group					
	Total VL cases (N = 81)		VL/HIV cases (N = 8)		Deaths due to VL (N = 7)	
	N	%	N	%	N	%
Sex						
Male	46	56.8	6	75.0	6	85.7
Female	35	43.2	2	25.0	1	14.3
Ethnic group						
Brown	40	49.4	4	50.0	6	85.7
White	29	35.8	2	25.0	-	-
Black	10	12.3	2	25.0	1	14.3
Ignored / blank	2	2.5	-	-	-	-
Residential area						
Urban	80	98.8	8	100.0	7	100.0
Rural	1	1.2	-	-	-	-
Age group (years)						
0 – 4	27	33.3	-	-	-	-
5 – 9	4	4.9	-	-	-	-
10 – 19	3	3.7	-	-	-	-
20 – 29	8	9.9	1	12.5	-	-
30 – 39	16	19.8	3	37.5	2	28.6
40 – 49	11	13.6	2	25.0	1	14.3
50 – 59	5	6.2	2	25.0	1	14.3
≥ 60	7	8.6	-	-	3	42.8
Educational level [‡]						
Illiterate or primary education (incomplete)	10	18.5	3	37.5	2	28.6
Primary education	17	31.5	4	50.0	2	28.6
Elementary education	7	13.0	-	-	1	14.2
Secondary education or higher education	11	20.4	-	-	-	-
Ignored / blank	9	16.6	1	12.5	2	28.6
Occupation [‡]						
Housewife or retired	16	29.6	4	50.0	3	42.8
Unemployed	7	13.0	3	37.5	3	42.8
Student	7	13.0	-	-	-	-
Building construction job	5	9.3	-	-	-	-
Self employed	4	7.4	-	-	-	-
Others	14	25.9	1	12.5	-	-
Ignored / blank	1	1.8	-	-	1	14.4
HIV co-infection						
Yes	8	9.9	8	100.0	2	28.6
No	66	81.5	-	-	5	71.4
Ignored / blank	7	8.6	-	-	-	-

[‡] Infants or young children aged 0 – 4 years (N=27) were not included in these variables.

VL/HIV cases (n = 8) and deaths due to VL (n = 7). The occurrence of disease prevailed among men (56.8%), brown-skinned individuals (49.4%) from the urban area of the municipality (92.6%). Although the median patient age was 31.1 years (range 0.3 to 81.3 years), children 0 to 4 years of age comprised most of the cases (33.3%), followed by adults 30 to 39 years of age (19.8%). Excluding children, VL was more frequent among individuals with low educational level. In addition, housewives or retired (29.6%), unemployed (13.0%) and students (13.0%) were the most affected occupational groups.

VL/HIV coinfection was observed in 9.9% of the autochthonous VL cases, although in 8.6% of the forms, this field was ignored or not filled. These subjects, as well as those who died due to VL, shared epidemiological similarities, mainly because they were predominantly male (75.0% and 83.3%, respectively), brown-skinned (50.0% and 83.3%), all urban residents, with low educational level, housewives or retired (50.0% and 37.5%), and unemployed (42.8%). The median patient age in the coinfecting and

mortality groups were higher, at 39.8 and 55.9 years, respectively, predominantly among those in the range of 30-39 (37.5%) and ≥ 60 (50.0%) years of age, respectively. Excluding patients with unknown HIV infection status, no significant difference was found in lethality related to VL between individuals who were VL/HIV coinfecting (25%, 2/8) and non-coinfecting (7.6%, 5/66) ($p = 0.163$) (data not shown).

Fever (95.1%), weakness (82.7%) and splenomegaly (79.0%) were the most common clinical manifestations among VL cases, although signs of severe disease were frequently observed, including jaundice (33.3%) and edema (18.5%). In VL/HIV coinfecting patients, there was a high frequency of bacterial infections (37.5%) and bleeding (25.0%), in addition to the classical manifestations. As expected, severe and diversified manifestations were observed among those patients who evolved to death due to VL. In this sense, bacterial infections (85.7%) ($p = 0.001$) and bleeding (71.4%) ($p < 0.001$) were significantly associated with death outcome (Table 2).

Table 2 – Frequency of clinical manifestations among the total cases of visceral leishmaniasis (total VL cases), VL/HIV coinfection (VL/HIV cases) and lethality due to VL (deaths due to VL) reported in the municipality of Rondonópolis, Mato Grosso State, Brazil, between 2011 and 2016

Clinical manifestation	Group											
	Total VL cases (N = 81)			VL/HIV cases (N = 8)				Deaths by VL (N = 7)				
	N	%	CI 95%	N	%	CI 95%	p-value ^a	N	%	CI 95%	p-value ^b	
Fever	77	95.1	87.6-98.4	8	100.0	67.6-100.0	1.000	7	100.0	64.6-100.0	1.000	
Weakness	67	82.7	73.1-89.4	7	87.5	52.9-97.8	1.000	6	85.7	48.7-97.4	1.000	
Splenomegaly	64	79.0	68.9-86.5	7	87.5	52.9-97.8	0.683	7	100.0	64.6-100.0	0.335	
Hepatomegaly	63	77.8	67.6-85.5	8	100.0	67.6-100.0	0.587	7	100.0	64.6-100.0	0.338	
Weight loss	63	77.8	67.6-85.5	7	87.5	52.9-97.8	0.677	6	85.7	48.7-97.4	1.000	
Pallor	62	75.3	66.3-84.4	6	75.0	40.9-92.9	0.985	6	85.7	48.7-97.4	0.675	
Jaundice	26	32.1	22.9-42.9	2	25.0	7.2-59.1	0.719	3	42.9	15.8-75.0	0.675	
Cough and/or diarrhea	25	30.9	21.9-41.6	2	25.0	7.2-59.1	1.000	2	28.6	8.2-64.1	1.000	
Bacterial infections	22	27.2	18.7-37.7	3	37.5	13.7-69.4	0.676	6	85.7	48.7-97.4	0.001*	
Edema	14	17.3	10.6-27.0	1	12.5	2.2-47.1	1.000	1	14.3	2.6-51.3	0.597	
Blood dyscrasias	8	9.9	5.1-18.3	-	-	-	-	1	14.3	2.6-51.3	0.981	
Bleeding	7	8.6	4.3-16.8	1	12.5	2.2-47.1	0.981	5	71.4	35.9-91.8	<0.001*	
Headache	2	2.5	0.7-8.6	-	-	-	-	-	-	-	-	
Abdominal distension	2	2.5	0.7-8.6	-	-	-	-	1	14.3	2.6-51.3	-	
Arrhythmia	1	1.2	0.2-6.7	-	-	-	-	-	-	-	-	
Itchy face	1	1.2	0.2-6.7	-	-	-	-	-	-	-	-	
Kidney and liver failure	1	1.2	0.2-6.7	-	-	-	-	1	14.3	2.6-51.3	-	
Pneumonia	1	1.2	0.2-6.7	-	-	-	-	1	14.3	2.6-51.3	-	

^aComparison of proportions of clinical manifestations between VL/HIV co-infected and non-co-infected VL patients. ^bComparison of proportions of clinical manifestations between VL patients who evolve to death and VL patients who do not. *Significant at Fisher exact test.

VL treatment was initially performed mainly with pentavalent antimonial in all cases (71.6%), with drug failure and cure reported in 7.4% and 71.6% of the patients, respectively. Liposomal amphotericin B was used to treat the majority (71.4%) of those who died due to VL, with only one (14.3%) drug failure report in this group. For VL/HIV cases, the use frequency of the two drugs was the same (50.0%). Drug failure and cure were reported in 12.5% and 62.5% of these patients, respectively (Table 3).

DISCUSSION

The current expansion of VL in Brazilian territories represents a clinical and epidemiological concern for public health authorities and health professionals, especially due to the complexity associated with its control and clinical management^{1,4,8}. The State of Mato Grosso is historically endemic for VL¹⁶, with the municipality of *Rondonópolis* containing almost half of the human cases reported there in recent years, being an area of intense VL transmission with regional and national relevance^{12,13}.

In this context, the geographical localization of the municipality is a topic that deserves attention. *Rondonópolis* is nearby and easily connected by transport routes to the municipality of Campo Grande, State of *Mato Grosso do Sul*, which previously emerged as a highly

endemic area in 2001¹⁷. Going North, *Rondonópolis* also represents the main path of entrance to the West Amazonian Basin, where some States with no reporting of autochthonous human VL cases, such as *Rondonia* and *Amazonas* are located¹⁸. Considering the possibility of vectors and reservoirs dispersion, as well as the intense demographic flow between these areas, *Rondonópolis* could contribute to the installation of human VL in these settings¹⁸⁻²⁰, as recently proposed by Sevá *et al.*²¹ in the State of *São Paulo*, Brazil.

Despite the observed decline in VL over the evaluated years, the incidence of the disease in *Rondonópolis* was considerable higher than the Brazilian average, which ranged from 1.6 to 2.0 new cases/100,000 inhabitants per year between 2011 and 2015²². Consequently, the absolute number of reported autochthonous cases also decreased with maintenance of high endemicity levels. This stabilization has also been noted in official data from Brazil between 2011 and 2015²³, and may be related to control measures along with lasting immunity developed in the affected populations, which probably generates herd immunity¹. However, considering the reemergence potential of VL, these observations should be interpreted with caution, since changes in the natural environment associated with favorable epidemiological conditions may lead to large outbreaks and epidemics²⁴.

Table 3 – Treatment aspects and outcomes related to the total cases of visceral leishmaniasis (total VL cases), VL/HIV coinfection (VL/HIV cases) and lethality due to VL (deaths due to VL) reported in the municipality of *Rondonópolis*, Mato Grosso State, Brazil, between 2011 and 2016

Variable	Group					
	Total VL cases (N = 81)		VL/HIV cases (N = 8)		Deaths by VL (N = 7)	
	N	%	N	%	N	%
Initial treatment						
Pentavalent antimonial	58	71.6	4	50.0	2	28.6
Liposomal amphotericin B	17	21.0	4	50.0	5	71.4
Amphotericin B deoxycholate	3	3.7	-	-	-	-
Ignored / blank	3	3.7	-	-	-	-
Drug failure						
Yes	6	7.4	1	12.5	1	14.3
No	71	87.7	6	75.0	6	85.7
Ignored / blank	4	4.9	1	12.5	-	-
Outcome[‡]						
Cure	73 [°]	90.2	6	75.0	-	-
Death by VL	7	8.6	2	25.0	7	100.0
Death by others causes	1	1.2	-	-	-	-

[‡] Information were checked at the Brazilian Mortality Information System. [°]The HIV infection status of seven of these patients was unknown.

On the other hand, lethality has been increasing in *Rondonópolis*, similar to observations in the State of Alagoas²⁵ and nationwide²⁶. In addition, the overall lethality rate in the present study (8.6%) was considerable and similar to the national average (8.1%)². Case fatality related to VL is usually the consequence of incorrect and/or late diagnosis⁵, drug toxicity⁶, delay in the management of patients who are at higher risk of progressing to death^{7,8}, presence of comorbidities such as malnutrition, cardiovascular diseases and immunosuppression, which may evolve to progressive and fatal weakness^{2,7,27}.

Indeed, in *Rondonópolis*, a high occurrence of patients with VL/HIV coinfection (9.9%) was found, a higher percentage than the one recently reported in Brazil, where the overall percentage of coinfection was approximately 8.5% in 2013²⁸. This is probably related to the increasing AIDS detection rate that has recently been observed in the municipality²⁹, and in other medium and small cities located in North and Central-Western Brazil^{30,31}. Thus, this pattern of occurrence of the HIV infection along with the urbanization of VL provided the geographical juxtaposition of both diseases^{4,30}. In *Rondonópolis*, this co-occurrence may have been enhanced because this city is a hub of regional entrenchment with accelerated demographic and socioeconomic flow³².

Although the observed case fatality among VL/HIV coinfecting patients who were investigated in the present study was statistically similar to the non-coinfecting, the absolute rate was higher, as similarly reported for the whole country¹⁰. The relationship between VL/HIV coinfection and VL lethality is not well elucidated because it is not known whether the severity is due to HIV infection or consequent opportunistic infections³³. Taken together, these findings reinforce the idea that lethality related to VL is a current major concern and underscore the need for improving the diagnosis and management of patients, including HIV infection screening^{10,33}.

Except for age groups, the epidemiological profile of VL in *Rondonópolis* did not differ substantially among the evaluated groups. Children aged 0 to 4 years were the most affected group among VL cases. This pattern was also described by several studies in Brazil^{11,34,35} and abroad^{36,37} and may be related to the fact that, when compared to adults, children have more contact with animal reservoirs and vectors, they have immature immunity and frequent nutritional deficits³⁸.

Surprisingly, there was no record of VL case fatality among children, as detected in other studies^{33,39}. This outcome was observed only in adults, especially among the elderly, where immunological decline occurs and comorbidities are more frequent^{33,39}. Indeed, VL/HIV

coinfection was observed exclusively in adults, which is expected due to the decreasing in HIV incidence among children, mainly due to improvements in the prevention of vertical transmission⁴⁰.

In relation to gender, men were the most affected. Although women are equally susceptible to the disease and fatality, this slight predominance may be related to behavioral differences due to the presence of men in areas at higher risk of phlebotomine sand fly bites^{35,41}. Furthermore, Guerra-Silveira and Abad-Franch⁴² demonstrated that the risk of VL is significantly male-biased during the first year of life, puberty, reproductive age and in elderly, corroborating with the high occurrence of the disease in these age groups herein detected. A lower proportion of VL/HIV coinfecting women was also described¹⁰ and corroborates the sex ratio of HIV/AIDS patients in the municipality of *Rondonópolis*, which was 1.4 cases in men for one case in women, in 2014²⁹.

The predominance of VL among urban residents is consistent with the expansion of the disease to large cities observed in Brazil since the 1980s, mainly due to demographic, environmental, and sanitary factors^{2,19}. In *Rondonópolis*, this process began in the 2000s and may have been influenced by the disorderly growth of the city, migration waves, accelerated population increase, expansion of agriculture, industrialization and the emergence of spaces with marked intra-urban differences⁴³, as detected in other regions of the country^{19,34,35,38}.

The higher occurrence and lethality of VL among individuals with low educational level has evidenced the socioeconomic vulnerability usually associated with VL⁴⁴, showing that a lack of schooling can influence health knowledge and practices focused on prevention⁴⁵. In this context, Borges *et al.*⁴⁶ demonstrated that increased schooling is a protective factor that reduced the risk of VL by 0.64-fold in the city of Belo Horizonte, Brazil.

Individuals who supposedly remained longer at home (minors and infants, housewives, retired, unemployed and students) were more affected by the disease. These findings suggest the importance of the intra and peri-domiciliary environments in the VL transmission cycle, where reservoirs and vectors are usually found^{45,47}.

The clinical manifestations of VL observed in the present study are concordant with those reported by other studies^{41,48}. Fever, weakness, hepatomegaly, weight loss and splenomegaly were frequent among VL cases and comprise the classic clinical features of the disease, generally found at the patients admission⁴⁹. Curiously, anemia and pancytopenia (blood dyscrasias) were not detected at high frequencies, although pallor was often reported. These signals are commonly associated with symptomatic VL^{50,51}

and are due to blood loss, erythropoiesis dysfunction, and/or up-regulated destruction of erythrocytes, among other factors^{41,52}.

On the contrary, jaundice, bacterial infections, edema and bleeding were often reported, especially among patients who died due to VL. These clinical scenarios are related to VL progression, poor prognosis^{7,48,53} and may indicate a late diagnosis; thus, it is essential that health professionals are aware of these signs, which are easily detected in early health services such as emergency care and basic health units^{35,48}.

Among VL/HIV coinfecting individuals, the clinical presentations of VL were similar to those found in VL cases. According to Lindoso *et al.*⁵⁴, this is usually verified in clinical practice, so that unusual manifestations tend to occur among patients with very low CD4+ T-cell counts⁵⁵. Unfortunately, the data in the present study did not allow us to check this relationship by assessing the level of these cells.

Due to its zoonotic nature in Brazil, VL treatment has a limited impact on disease transmission, but is essential for the patient¹⁵. However, the available arsenal remains scarce, in addition to presenting problems related to acceptance, efficacy, side effects and high cost^{6,56}. Similar to observations by Petrela *et al.*⁵⁷, pentavalent antimonial was the first-line drug for the treatment of most autochthonous cases in *Rondonópolis*, with low drug failure. Indeed, meglumine antimoniate at 20 mg/kg/day for 20-40 days has been the standard treatment for VL in Brazil, with no report of drug resistance and high cure rates¹⁵. However, due to the risk of adverse effects such as cardiotoxicity, pancreatitis and nephrotoxicity, patients should be monitored or hospitalized during therapy⁵⁸.

In this sense, liposomal amphotericin B is recommended as the first choice for the treatment of VL patients with nephropathies and heart diseases in Brazil, as well as individuals who are over 50 years of age, immunosuppressed and with signs of severe VL disease⁵⁹. The lipid formulation assures the delivery of large drug doses in less time with low toxicity⁶⁰. Taken together, the national recommendations support our observation of the increased use of liposomal amphotericin B among VL/HIV coinfecting patients and in those who died in the municipality of *Rondonópolis*.

The main limitation of the present study was the use of secondary data, which is susceptible to lack of information. Nevertheless, our investigation presents an important epidemiological and clinical overview of the occurrence, VL/HIV coinfection and lethality due to VL in the municipality of *Rondonópolis*, which represents an important endemic Brazilian area with intense transmission. Thus, these data may be useful to help the planning of

integrated public health policies focused on VL prevention, early detection and patients' management. Moreover, the results of this study also demonstrated the need for future and more robust investigations involving humans, reservoirs and vectors in the area.

ETHICAL APPROVAL

This study was approved by the Ethical Committee for Human Research of *Júlio Müller* University Hospital (CAAE N° 52023215.5.0000.5541).

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