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RESEARCH ARTICLE

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PREVALENCE OF LEISHMANIASIS-HIV COINFECTION IN BRAZIL FROM 2007 TO 2018

***Daniela Soares Leite**

Department of Morphology and Physiological Sciences, State University of Pará, Marabá, Brazil

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*Corresponding author: Daniela Soares Leite,

ABSTRACT

The number of cases of Visceral Leishmaniasis-HIV coinfection has increased, and the association between the two infections is already considered an emerging problem. The aim was to describe the clinical and epidemiological profile of cases of coinfecting VL-HIV in Brazil. This is a descriptive study of confirmed cases of VL-HIV co-infection, notified in Brazil, in the years 2007 to 2018. The variables studied were: date of notification; age; sex; race / color; schooling; Region; HIV coinfection and case evolution. All collected data were entered into a Microsoft Excel® 2010 spreadsheet and were analyzed using Bioestat statistical software, version 5.0, chi-square test ($p < 0.01$). 45,055 cases of VL from 2007 to 2018 were confirmed in the country and 7.5% (3,388 / 45,055) were coinfecting with HIV. It was observed that the coinfecting VL-HIV patients were male (78.2%); 39.8% had elementary education; the predominant age group was 20-39 years (49.2%); they belonged to the brown / black race (76.2%) and evolved to cure (65.7%). It is necessary that health professionals, especially those working in areas where VL is endemic, pay attention to the occurrence of VL-HIV co-infection, considering the high number of cases in which HIV spreads to medium and small cities.

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INTRODUCTION

Visceral leishmaniasis (VL), or kala-azar, is a neglected tropical disease that, if left untreated, can have a high lethality in humans, around 10 to 20%. Often, death is caused by bacterial infections and / or hemorrhages (Ortiz and Anversa, 2015). It is caused by species of the genus *Leishmania*, belonging to the *Leishmania (Leishmania) donovani* complex. In Brazil, the etiologic agent is *L. chagasi*, a species similar to *L. infantum* found in some Mediterranean and Asian countries (Gontijo and Melo, 2004), that is transmitted to humans through the sting of the female phlebotomine insect, *Lutzomyia longipalpis* (Coutinho *et al.*, 2017). More than 90% of the cases registered in the world occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan (WHO, 2020). VL occurs in 12 countries of Latin America, with 96% of cases reported in Brazil (Lindoso *et al.*, 2014). In Brazil, the first recorded case of VL occurred in 1913 and until 1970 it was an essentially rural disease with domestic and peri-domestic transmission and with about 90% of cases being reported in the Northeast region, however since the 1980s there has been an expansion to other regions (especially the Southeast), both in

magnitude and geography, becoming a serious problem in urban areas, including large cities. The high prevalence of the disease has been observed in urban areas and this phenomenon can be attributed to high population density, increased migration, environmental changes, inadequate population living conditions and adaptation of the vector to the urban environment (Costa *et al.*, 2018; Rodrigues *et al.*, 2017). VL has regained medical importance, due to factors such as the emergence of the acquired immunodeficiency syndrome epidemic and urbanization of vectors, due to the disordered occupation of urban spaces and deforestation in rural areas. Infection with the human immunodeficiency virus (HIV) is considered of great importance for Public Health due to its magnitude, because, according to the World Health Organization (WHO), both infections are among the most relevant events in the world: VL occurs in 88 countries, 72 of which are developing countries (Cavalcante and Vale 2014), with approximately 500,000 new cases and 59,000 deaths per year; and an estimated 37.9 million [32.7 million — 44.0 million] people worldwide are infected with HIV (Sousa-Gomes *et al.*, 2011; UNAIDS, 2020). The first case of *Leishmania*-HIV coinfection was described in 1985, in southern Europe, and currently, it is registered in 35 countries.

The first American Leishmania-HIV-coinfected patient was reported in Brazil 05 years after the first world report in southern Europe (Lindoso *et al.*, 2014). A significant increase in the number of cases has been observed since the beginning of the 1990s, and a continual increase is predicted due to the geographical overlap of these infections as a result of the urbanization of leishmaniasis and ruralization of HIV infection. It is estimated that 25-70% of adults with VL are coinfecting with HIV, prompting some authors to support the inclusion of VL as an opportunistic infection, indicative of acquired immunodeficiency syndrome (AIDS). Coinfection has particular aspects in terms of clinical presentation, diagnosis, and response to specific treatment; moreover, early diagnosis is essential to reduce both disease severity and mortality. (Coutinho *et al.*, 2017; Sousa-Gomes *et al.*, 2011). In the early 1990s, a higher incidence of VL-HIV coinfection was observed in the Mediterranean basin, which peaked in 1997 and, thereafter (1998–2001), a plateau was observed and only from 2001, there was a progressive decrease in VL-HIV cases in this region, and currently the incidence is low, mainly due to the use of highly active antiretroviral therapy (HAART). On the other hand, there is an increase in VL-HIV coinfection in other geographical areas, such as in Ethiopia, where the incidence rates of VL-HIV coinfection are very high. In Latin America, especially in Brazil, VL-HIV coinfection has steadily increased. Currently, the prevalence of HIV infection in patients with VL is 9% (Lindoso *et al.*, 2018). The number of cases of VL-HIV coinfection has increased, and the association between the two infections is already considered an emerging problem. In southern European countries, for example, this picture is significant. More than 70% of VL cases in adults are related to AIDS and 9% of all AIDS patients suffer from newly acquired VL (Malafaia, 2009). The coexistence of the two diseases causes their effects to be enhanced, LV accelerates the emergence of AIDS in individuals infected with HIV, leading to cumulative immunosuppression and stimulating the replication of the virus. On the other hand, in areas endemic for VL, AIDS increases the risk of the disease by 100 to 1,000 times (Gomes, 2012). Coinfection promotes changes in the immune system, which causes the clinical evolution of HIV and VL to accelerate. Individuals infected, but asymptomatic, with *Leishmania donovani*, *L. infantum* or *L. chagasi*, species that cause VL, and who have HIV infection, are groups at risk for the development of severe forms of the disease (Coelho Junior *et al.*, 2016). Although the mortality rate due to infectious and parasitic diseases (PID) has shown a sharp decline in recent years, it is observed in Brazil that these diseases still play an important role among the causes of death. And there is a direct relationship between its occurrence and the Human Development Index - HDI (Araújo, 2015 Brasil, 2019). It is therefore justified to carry out this study whose objective is to describe the prevalence and the clinical and epidemiological profile of cases of VL co-infected with HIV (VL-HIV) in Brazil.

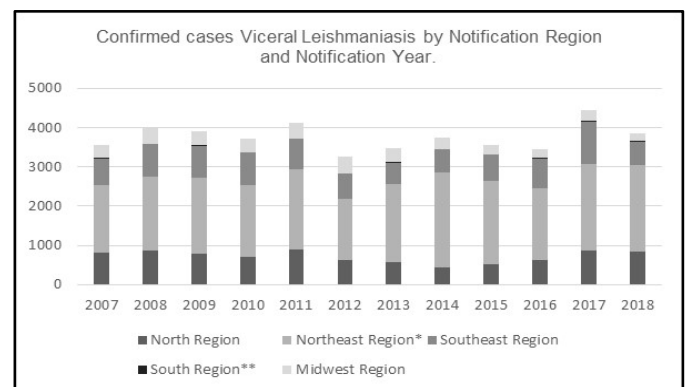
METHODOLOGY

Descriptive study of confirmed cases of VL coinfecting with HIV, regardless of having developed AIDS, reported in Brazil, in the years 2007 to 2018. The study area was Brazil and its five Regions (Federative Units) and the data source used were the confirmed cases of VL registered in the Information System for Notifiable Diseases - Sinan Net / Ministry of Health / SVS, made available in DATASUS. The studied variables were: date

of notification; age; sex; race / color; schooling; Region; HIV coinfection and case evolution. Confirmed diagnoses of VL and sera-agents for HIV were included. The incidence of VL in Brazil (confirmed cases / population in each region of the study) and the incidence of HIV coinfection among the confirmed cases of VL (number of cases of HIV coinfection / number of LV cases in each region) were calculated. All collected data were entered into a Microsoft Excel® 2010 spreadsheet and were analyzed using Bioestat statistical software, version 5.0. The categorical variables were described as absolute and relative frequencies and compared by means of the chi-square test. P-values below 0.01 were considered significant. As it is a public domain system (DATASUS), the study was not submitted to the Human Research Ethics Committee.

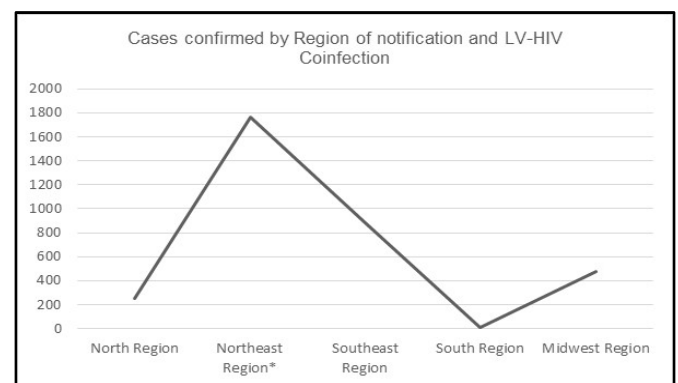
RESULTS

45,055 cases of VL were confirmed from 2007 to 2018, in all regions of the country. The Northeast Region was the region with the highest prevalence. Regarding the distribution of prevalences over the years studied, the regions did not follow the same pattern of increase in cases over the years (Graph 1). Of the total confirmed cases during the study period, 7.5% (3,388 / 45,055) were coinfecting with HIV (Graph 2). The prevalence of VL, per 100,000 inhabitants, in each of the five Regions of the country, over the years analyzed (2007 to 2018) can be seen in the graph below (Graph 3).



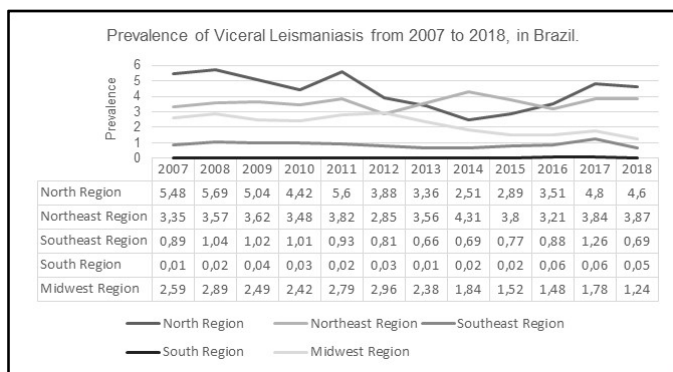
Source: Ministry of Health / SVS - Information System for Notifiable Diseases - Sinan Net. *Chi-Square Adherence
Test * $p < 0,001$ ** $p = 0,0013$

Graph 1. Confirmed cases Visceral Leishmaniasis by Notification Region and Notification Year

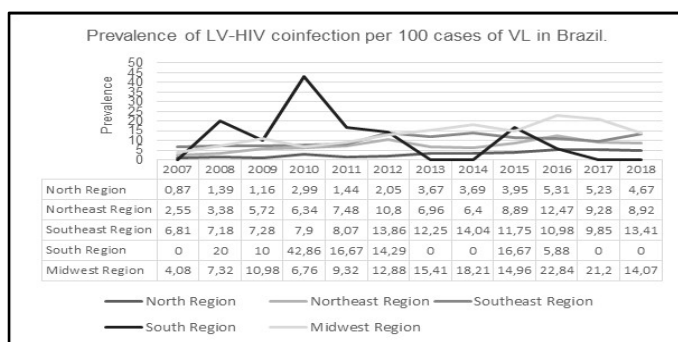


Source: Ministry of Health / SVS - Information System for Notifiable Diseases - Sinan Net. *Chi-Square Adherence
Test * $p < 0,001$

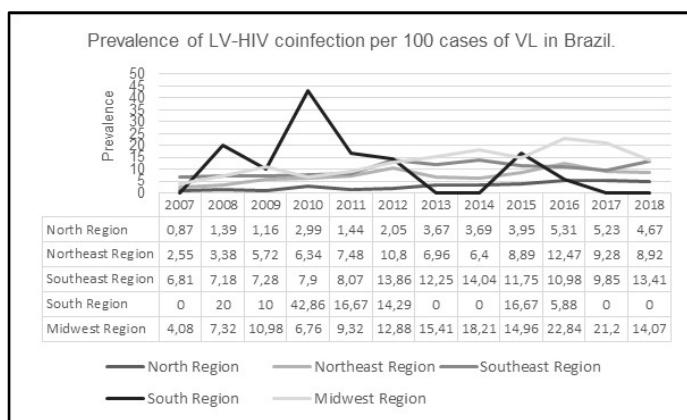
Graph 2. Cases confirmed by Region of notification and LV-HIV Coinfection



Graph 3. Prevalence of Visceral Leishmaniasis, per 100,000 inhabitants, in the period from 2007 to 2018, in the five regions of Brazil



Graph 4. Prevalence of LV_HIV / LV coinfection, per 100 cases of VL, from 2007 to 2018, in the five regions of Brazil



The North Region had its highest prevalence in 2008 (5.7) and the lowest in 2014 (2.5); the Northeast Region had its highest prevalence in 2014 (4.3) and the lowest in 2012 (2.8); the Southeast Region had its highest prevalence in 2017 (1.3) and the lowest in 2013 (0.6); the Midwest Region had its highest prevalence in 2012 (3.0) and the lowest in 2018 (1.2); and the South Region had an prevalence close to zero during the analysis period. The prevalence of LV-HIV coinfection, per 100 cases of VL, can be seen in Graph 4. The North Region had the lowest total incidence of LV_HIV / LV coinfection while the Midwest Region had the highest total incidence for the analyzed period. With regard to the epidemiological variables analyzed, it was observed that VL-HIV coinfecting patients were predominantly male and represented 78.2% of the cases, and women (21.8%); 39.8% of all LV-HIV coinfecting had elementary education; the predominant age group was 20-39 years (49.2%); they belonged to the brown / black race (76.2%) and evolved to cure (65.7%) (Table 1).

Table 1. Epidemiological variables of LV-HIV coinfecting individuals from 2007 to 2018, in Brazil

Variables	N	%
Gender		
Male	2649*	78,2%
Female	738	21,8%
Education	N	%
Not applicable	168	5,0%
Illiterate	116	3,4%
Elementary ^(a)	1347*	39,8%
High School ^(a)	430	12,7%
higher education ^(a)	72	2,1%
unknown	1255	37%
Age	N	%
<10	203	6%
10-19	92	2,7%
20-39	1668*	49,2%
40-59	1268	37,4%
>60	155	4,6%
unknown	2	0,05%
Race	N	%
White	532	15,7%
Brown/Black	2582*	76,2%
Indian	08	0,23%
Mongoloid	12	0,35%
unknown	254	7,5%
Evolução	N	%
Cure	2226*	65,7%
Abandonment	46	1,35%
Death by VL	318	9,4%
Death by other causes	280	8,3%
Transfer	161	4,8%
unknown	357	10,5%

*Chi-Square Adherence Test * p <0.0001 a

DISCUSSION

From 2007 to 2018 of the total confirmed cases of VL in the period, 3,388 (7.5%) were coinfecting with HIV. The percentage of coinfecting VL-HIV observed here is higher than values found in other studies in the country; Sousa-Gomes *et al.*, 2011 found 3.7% in the study period (2007-2008), while Sousa-Gomes, 2012 found 2.1% in the study period (2001-2010). The analysis shows that there was an increase in the number of people coinfecting when compared with studies from previous periods, which denotes an increasing trend of this coinfection. When analyzing the geographical distribution of cases of VL-HIV coinfection by Region, there is notification of the disease in all Brazilian regions. What is expected, since there has been a significant increase in the number of cases since the early 1990s, and this increase and establishment was predicted due to the geographical overlap of these infections, as a result of the urbanization of leishmaniasis and the ruralization of HIV infection (Coutinho *et al.*, 2017; Sousa-Gomes *et al.*, 2011; Sousa-Gomes, 2012). However, despite notifications in all regions, the predominance of cases occurred in the Northeast Region, followed by the Southeast Regions, following the prevalence of VL and AIDS in these regions. Over the years, the incidence of VL_HIV / LV coinfection varied within each Region, and the total incidence was higher in the Midwest Region and lower in the North Region. What differs from the pattern of incidence of VL in the regions, where the North Region showed a higher total incidence of VL and the South Region, lower, in the study period.

The distribution of cases was predominant in males (78.2%), maintaining the pattern found for cases of VL-HIV in Brazil; Sousa-Gomes *et al.*, 2017, found a frequency of 74.8% and Coutinho, *et al.*, 2017, 80.7%. The percentage of coinfecting

patients with complete or incomplete primary education was 39.8%, similar to that observed by Coutinho, *et al*, 2017 (40%) and by Sousa-Gomes *et al.*, 2011 (38.8%). However, the high percentage of ignored / blank cases for education in the present study (37%) is noteworthy. Low education is a reality in many municipalities in Brazil, which influences self-care of health, in the awareness that each patient is a health-promoting agent for himself and for the community (Nascimento, 2014). The prevalence of coinfection was higher in the 20-39 age group (49.2%); Coutinho, *et al*, 2017, found a frequency of 88.4% for the 18-50 age group and Sousa-Gomes *et al.*, 2011, 77.7% for the 20-49 age group. Regarding race, there was a predominance of browns / blacks (76.2%); Coutinho, *et al*, 2017, found a frequency of 92.3% of mixed race and Sousa-Gomes *et al.*, 2011 (57.9%). During the course of the disease, 65.7% of those notified with LV-HIV co-infection, evolved to cure. LV-HIV coinfection predominates in adult men aged 30 to 50 years, reflecting the patterns of HIV / AIDS infection in the country (Coelho Junior *et al.*, 2016). In Brazil, the expansion of the geographical distribution area of acquired immunodeficiency syndrome (AIDS) and its expansion to the poorest sections of the population and the growing urbanization of LV, indicates that the prevalence of LV-HIV coinfection should remain high in the coming years. It is necessary that health professionals, especially those working in areas where VL is endemic, pay attention to the occurrence of LV-HIV co-infection, considering the high number of cases where HIV has spread to small and medium-sized cities. The imbalance in the health-disease process is not linked only to the act of becoming ill, Langdon, 2014 says that the socioeconomic structure determines the health situation of the populations. Based on this fact, socioeconomic factors interfere with the degree of success in implementing preventive measures and adherence to treatment, degrees of exposure and popular participation in prophylactic actions that are fundamental to the success of control strategies.

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