Visceral leishmaniasis relapse: what do we know and what should we learn from Brazilian episodes reported from 2014 to 2020?

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https://doi.org/10.1590/SciELOPreprints.16059

Submitted on: 2026-05-06
Posted on: 2026-05-07 (version 1)
(YYYY-MM-DD)

Visceral leishmaniasis relapse: what do we know and what should we learn from Brazilian episodes reported from 2014 to 2020?

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Abstract

There is a lack of knowledge regarding the eventual differences in the clinical and sociodemographic characteristics comparing VL relapse events with new onset VL events. We analyzed the clinical and epidemiological profile of new occurrence and relapse events in patients with VL in Brazil over the 2014-2020 period, using linked databases of VL and HIV/AIDS cases from the Notifiable Diseases Information System (SINAN), the Logistics Control System for Medications (SICLOM) and the Laboratory Test Control System (SISCEL) for HIV/AIDS. New VL case event was defined as VL reported in patients with no previous registry of VL during the past 12 months. Relapse event was defined as VL reported in patients with previous registry of VL during the past 12 months after the cure. Between 2014 and 2024, 23,025 VL events were reported, 93.75% were recorded as new case events and 6.25% as relapse events. When comparing the new case to relapse events, we observed that, respectively: 66% and 70% of patients were male, ($p = 0.003$); 43% and 34% were under 15 years of age ($p < 0.001$); and 41% and 43% had education up to high school ($p < 0.001$). Symptoms such as fever, weakness, weight loss, pallor, and jaundice were more frequent in new case than in relapse events ($p < 0.05$). Relapses were

proportionally more frequent in patients co-infected with VL/HIV (41%) compared to new cases (11%) ($p<0.001$). Among HIV coinfected patients, $CD4^+/CD8^+$ T lymphocyte count and median HIV viral load were significantly lower in relapse events. To better understand such differences in new and relapse cases, in depth prospective studies to identify factors associated with relapse in VL patients are essential.

Keywords: Relapse, visceral leishmaniasis, HIV

Introduction

Visceral leishmaniasis (VL) is one of the most severe neglected diseases listed by the World Health Organization's (WHO). Although its incidence has been declining in Brazil, the disease still poses a significant burden due to its severity and widespread impact (Soares et al., 2025).

In Brazil, suspected cases of VL are reported to the Notifiable Diseases Information System (SINAN), with the case entry type being classified as a “new case” or “relapse”. A patient may be reported in the system more than once in the same year or period, requiring thorough and periodic verification by municipal, state, and federal health teams to identify possible duplicates or inconsistencies (Brasil, 2026).

For health authorities, the main priority is proper patient management, including early diagnosis and adequate treatment, to prevent disease progression, relapses, and fatal outcomes (Ministério da Saúde, 2023).

Relapse in visceral leishmaniasis is considered a risk factor for death; however, few studies have evaluated the epidemiological and clinical characteristics of relapse events and the factors associated with its occurrence (Costa et al., 2023; Simão et al., 2020)

HIV/AIDS is the most significant immunodeficiency in humans today, leading to impaired cellular immunity, especially involving $CD4^+$ T lymphocytes. In HIV/VL coinfected patients, this immune dysfunction is further exacerbated, resulting not only in a marked reduction of $CD4^+$ T cells but also in persistent high parasitic load throughout clinical follow-up (Alexandrino-de-Oliveira et al., 2010;

Cipriano et al., 2017; Cota et al., 2014; Kuschnir et al., 2021; Leite de Sousa-Gomes et al., 2017).

In public health surveillance, VL relapse is defined as the return of symptoms within 12 months after clinical cure (Brasil, 2014). This time frame is used to distinguish “true” relapse from “new” infection, helping to better define the disease's epidemiological profile and streamline health service workflows. However, the lack of validated criteria to distinguish between new infection and relapse is a significnt limitation. Then, it is important to clarify both the operational criteria used by health services to classify a relapse and the clinical concept underlying it.

Analyzing the reported relapse events and comparing them with new case events at presentation leverages the SINAN database structure by including all events occurring during the study period, providing a descriptive assessment that captures the full scope of reported cases. Thus, this study aimed to describe the epidemiological profile of new cases or relapse events of VL in Brazil from 2014 to 2020, using linked databases.

Methodology

This is a cross-sectional study of the whole reported VL events in Brazil during a seven-year period.

New case definition

A new case was defined as VL reported in patients with no previous registry of VL, or a patient with a new infection documented after 12 months of clinical cure.

Relapse definition

The operational definition of relapse was the recurrence of symptoms up to 12 months after clinical cure.

VL-HIV coinfected case

VL patients were considered coinfected with HIV if they met at least one of the following criteria: 1. Explicit record of HIV coinfection in the VL database; 2. Notification as a HIV case in the SINAN-HIV database; 3. Inclusion in the registry

database of patients undergoing follow-up or treatment for HIV (SISCEL e SICLOM).

Study population

The study population consisted of confirmed VL cases with entry types classified as new case or relapse from 2014 to 2020, obtained from the Notifiable Diseases Information System (SINAN).

Data sources

SINAN comprises all compulsorily notifiable diseases, as described in official regulation. The notification forms have three domains that are similar across all diseases: 'general data', 'individual notification', and 'residence data'. The specific data, considered complementary, will be described below for each database used.

SINAN VL database

Includes 25 variables, of which 19 are mandatory. It includes variables related to the types of clinical and laboratory diagnosis (parasitological and immunological), case treatment (type of medication, dose, treatment start date), case confirmation criteria, as well as disease progression (cure, death due to VL, death due to other causes, and transfer).

SINAN HIV database

Includes 18 variables, all of which are mandatory. It includes variables related to the probable mode of infection, laboratory diagnosis, AIDS case classification criteria, and case treatment, as well as disease progression (alive, death due to HIV, and death due to other causes).

SISCEL e SICLOM databases

SISCEL is the laboratory test control system for CD4+/CD8+ and HIV viral load, developed to facilitate the history of CD4+ T-lymphocyte count and HIV viral load testing. It has two distinct forms: one for requesting viral load testing (comprising 54 variables, of which 30 are mandatory) and another for CD4+ T-lymphocyte counting (comprising 52 variables, of which 26 are mandatory).

SICLOM is the logistics management system for antiretroviral drugs. All patients undergoing HIV treatment must be registered in SICLOM to receive antiretrovirals. In addition to inventory control and drug distribution, SICLOM monitors clinical and laboratory information on HIV/AIDS patients and the use of different therapeutic regimens. It comprises 33 variables, of which 13 are mandatory.

To identify cases of HIV coinfection, adding relevant clinical and immunological data we used the database consolidated by the Department of HIV/AIDS, Tuberculosis, Viral Hepatitis, and Sexually Transmitted Infections, based on records from SINAN, the Laboratory Tests Control System (SISCEL), and the Logistics Control System for Medications (SICLOM).

Database linkage

Initially, the VL database was linked to the SINAN-HIV database using a deterministic approach with composite key consisting of the patient's first and last name, date of birth, and mother's name.

Next, the resulting database was linked to the follow-up databases for people living with HIV (SICLOM and SISCEL). This step involved a many-to-many linkage, as the same patient could have more than one record in the VL database, and the same patient could also have multiple records in the medication dispensing and laboratory test databases over time.

For the analysis, we selected records from SICLOM and SISCEL in which the medication dispensation date or laboratory test collection date was closest to the VL notification date, to represent the patient's clinical and immunological status closest to the time of the VL episode.

Variables of interest

There following demographic variables were assessed: age (years), sex, and education level. Clinical variables included the presence or absence of jaundice, lymphadenopathy, edema, ascites, hepatosplenomegaly, associated infectious condition, hemorrhagic phenomena, pallor, cough, diarrhea, weight loss, fever, weakness, and HIV coinfection.

Additionally, laboratory confirmation methods included parasitological diagnosis, indirect immunofluorescence (IIF), and other tests such as serological

tests (e.g., ELISA), molecular tests (e.g., PCR), and immunochromatographic tests, disease outcome (cure, death from VL, death from other causes, treatment abandonment, and transfer to other healthcare service), treatment timeliness calculated in two ways: the period between treatment and symptom onset dates; and the period between treatment and notification dates, initial drug administered, and drug used in case of therapeutic failure underwent assessment.

Statistical analysis

Each notification was treated separately; there was no merging of data from different notifications for the same individual. Therefore, the data represents the profile of the set new case and recurrence events of VL.

Categorical variables were described using absolute and relative frequencies, while quantitative variables were described using mean and standard deviation or the median and interquartile range, considering the asymmetry of the distributions.

To compare the characteristics of new case and relapse events the Pearson's chi-square test was used when expected frequency assumptions were met; otherwise, Fisher's exact test was applied, for categorical variables, and the Wilcoxon-Mann-Whitney test (Wilcoxon rank-sum test) for quantitative variables.

For variables that display overdispersion, the trimmed mean was applied to reduce the likelihood of inconsistencies.

All tests were performed with a significant level of 5% ($\alpha = 0.05$). Analyses were conducted using R software (R Core Team), version 4.4.1, running on the aarch64-apple-darwin20 platform (macOS, ARM architecture). The integrated development environment used was RStudio (Posit Software, PBC), version 2026.01.0+392.

Ethics Committee in Human Research

This study was approved by the Ethics Committee in Human Research from University of Brasília (Brasília, Brasil), with the approval number 60492022.4.0000.5558.

Results

From 2014 to 2020, 23,025 VL events were reported. Of these, 93.75% (21,596) were classified as new case events and 6.25% (1,429) as relapse events.

The linkage between all databases was made to supplement records of HIV coinfection that may not have been directly reported in the SINAN notification form. VL/HIV coinfection was proportionally more frequent among relapses, 40.8%, when compared to new cases, 10.6%. We observed that 18.6% of new cases and 7.5% of relapses events records have the HIV status recorded as unknown. Among VL/HIV coinfected events, the proportion of relapses were higher (20.2%) than among VL/HIV non-coinfected events (4.6%) (p<0,0001) (Table 1).

Table 1. VL/HIV coinfection, by type of entry, in Brazil, 2014-2020.

Characteristic	Overall (N = 23,025)[1]		New case events (N = 21,596)[1]		Relapse events (N = 1,429)[1]	
VL/HIV coinfected	N	%	N	%	N	%
Yes	2877	12.2	2293	10.6	584	40.8
No	16,020	69.5	15,282	70.7	738	51.6
Ignored	4,128	17.9	4,021	18.6	107	7.5

[1]n (%)

[2]Pearson's Chi-squared test

[3] Linkage performed using data from the SINAN VL and HIV databases

[4] Linkage performed using data from the SINAN VL, HIV, SICLON and SISCEL databases

The median of new case events was 3,085 and 204 for relapses events. The year 2017 had the highest number of new VL case events recorded, with a decrease observed from that year onward. The highest number of relapse events occurred in 2018, with a 26% reduction by 2020 (Supplementary file - Figure 1).

Regarding demographic variables, only sex is mandatory in the SINAN notification form, while age and education level are considered essential variables. Stratified by entry type (new case vs. relapse, respectively), 66% and

70% of the events occurred among male (p = 0.003); 43% and 34% in children and teenagers under 15 years of age (p < 0.001); and 57% and 49% had education up to high school level (p < 0.001) (Table 2). The age group of under fifteen years concentrated the highest number of events, both for new cases (43%) and relapses events (34%).

Table 2. Comparison of demographic variables of VL new case and relapse events, Brazil, 2014 to 2020.

Characteristic	Overall (N = 23,025)[1]		New case event (N = 21,596)[1]		Relapse event (N = 1,429)[1]		p-value[2]
Sex	**Total**	**%**	**Total**	**%**	**Total**	**%**	0.003
F	7800	33.8	7367	34,1	433	30,3	
M	15225	66.1	14229	65,9	996	69,7	
Age	**Total**	**%**	**Total**	**%**	**Total**	**%**	<0.001
<15	9744	42.3	9263	42,9	481	33,6	
15-24	2298	9.9	2229	10,3	69	4,8	
25-34	2688	11.6	2514	11,6	174	12,2	
35-44	2900	12.6	2612	12.0	288	20,1	
45-54	2352	10.2	2118	9,8	234	16,3	
55+	3043	13.2	2860	13,2	183	12,8	
Education Level	**Total**	**%**	**Total**	**%**	**Total**	**%**	<0.001
Unknown/Not applicable	13,199	57.3	12,405	57.4	794	55.5	
Up to 4th grade (Primary/elementary education)	3,953	17.1	3,749	17.3	204	14.2	
Up to 8th grade (Lower secondary/Middle school)	3,433	14.9	3,196	14.8	237	16.6	
Up to High school (Upper secondary)	2,173	9.4	2,006	9.2	167	11.7	
Up to Higher education (University/College)	267	1.1	240	1.1	27	1.9	

[1]n (%)

[2]Pearson's Chi-squared test

Regarding clinical signs, we observed that for most of them there is a statistically significant difference between new cases and relapses. Of the 11

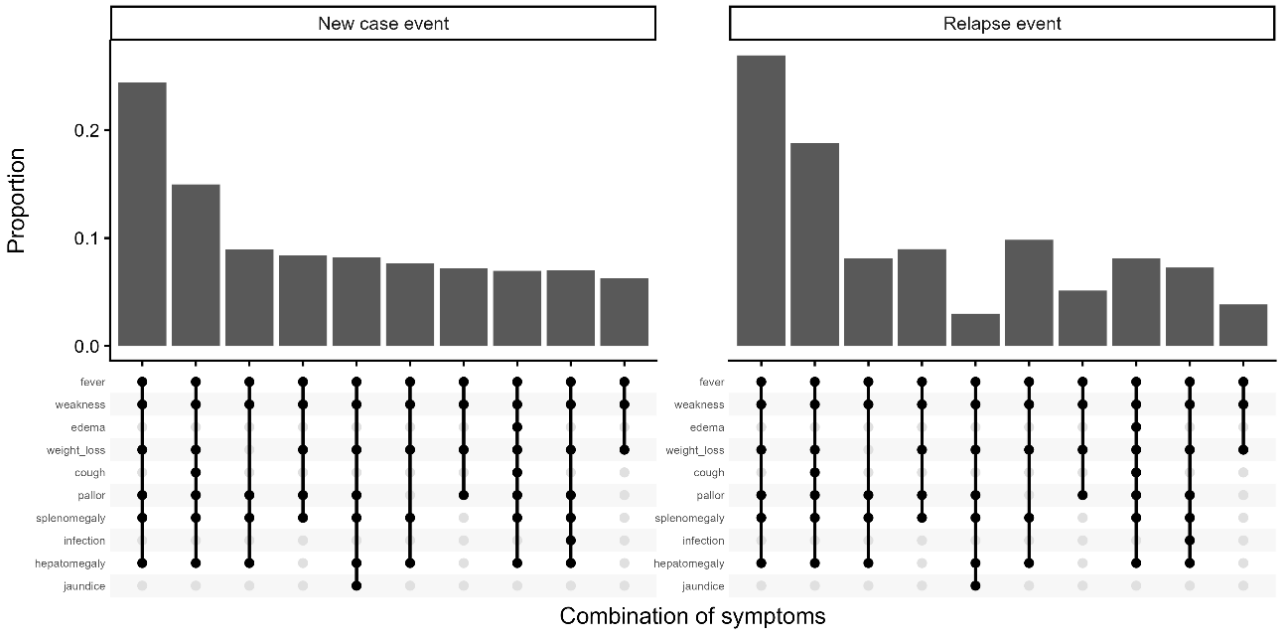
clinical signs present in the notification form, only four (hepatomegaly, splenomegaly, infectious condition, and hemorrhagic phenomena) showed no difference between the new and relapse events (Supplementary file - Figure 2).

Among the clinical signs statistically associated with the type of entry (new case vs. relapse), fever, weakness, weight loss, pallor, and jaundice stand out, all significantly more frequent among new cases than in relapses. For new case and relapse events, respectively, fever was present in 92% and 77% ($p < 0.001$); weakness, in 79% and 72% ($p < 0.001$); edema, in 26% and 21%; weight loss, in 70% and 62% ($p < 0.001$); pallor, in 72% and 69% ($p = 0.011$); and jaundice, in 25% and 15% ($p < 0.001$) (Supplementary file - Figure 2).

Conversely, the absence of these symptoms was proportionally more frequent among relapse events. Furthermore, the presence of other types of signs and symptoms, other than the classic ones described here, occur more frequently in relapses (29%) than in new cases (25%) ($p = 0.002$).

Figure 1 shows the ten most frequent combinations of signs and symptoms presented in new cases and relapses events. In both groups, the most frequent combination corresponds to a broad clinical picture, characterized mainly by the concomitant presence of fever, weakness, weight loss, pallor, and hepatosplenomegaly. This combination is the most frequent among both new cases and relapses, although its relative frequency is slightly lower in the relapse group. The second most frequent combination, also common to both groups, includes practically the same set of signs and symptoms, with minor variations, such as the inclusion or exclusion of certain additional symptoms, like cough.

Figure 1. Ten most frequent clinical signs combinations of VL new case and relapse events, Brazil, 2014 to 2020.



Regarding diagnostic procedures, Table 3 shows the differences in proportions between the type of entry and the diagnostic methods used. Parasitological tests were most often used in relapses, occurring in 46% of these events, whereas among new cases this proportion was 29%. Concerning the indirect immunofluorescence test (IIF), a statistically significant difference between the type of entry was also identified (p=0.010). Although testing is frequent in both groups, it was proportionally less common among relapses, in which 21% of events had a positive IIF, compared to 32% in new cases.

Conversely, for the other kinds of diagnostic methodologies, like rapid test, ELISA and PCR, no evidence of a statistically significant difference between the type of case entry was observed (p-value = 0.8). The presence of this type of diagnostic criterion occurred in similar proportions between new cases and relapses, 49% and 42%, respectively.

Regarding the choice of medications used in the initial treatment of VL, among new cases, a predominance of pentavalent antimonial use was observed, employed in 50% of events, followed by liposomal amphotericin B (25%) and conventional amphotericin B (9%). In contrast, among relapses, liposomal amphotericin B was the most frequently used drug, corresponding to 54% of events, while the use of pentavalent antimonial was substantially lower, occurring

in 23% of relapses. The use of conventional amphotericin B showed similar proportions between the groups, with 9% in new case and 11% in relapse events, while the category "other or not used" was less frequent among relapses (Table 3).

A significant difference was observed between new case and relapse events in therapeutic failure ($p<0.001$) (Table 3).

Table 3. Characteristics of diagnostic procedures and treatment of VL new case and relapse events in Brazil, 2014-2020.

Characteristic	Overall (N = 23,025)[1]		New case event (N = 21,596)[1]		Relapse event (N = 1,429)[1]	
Parasitological test	**N**	**%**	**N**	**%**	**N**	**%**
No	1,745	7.5	1637	7.5	108	7.5
Yes	6,933	30.1	6266	29.0	667	46.6
Not done[3]	14,347	62.3	13693	63.4	654	45.7
IIF	**N**	**%**	**N**	**%**	**N**	**%**
No	1,836	7.9	1,734	8.0	102	7.1
Yes	7,232	31.4	6,931	32.0	301	21.0
Not done[3]	13,957	60.6	12,931	59.8	1,026	71.8
Other diagnostic procedure	**N**	**%**	**N**	**%**	**N**	**%**
No	2,306	10.0	2,179	10.1	127	8.89
Yes	11,368	49.3	10,754	49.8	614	42.97
Not done[3]	9,351	40.6	8,663	40.1	688	48.15
Primary treatment	**N**	**%**	**N**	**%**	**N**	**%**
Pentavalent antimonial	11,137	48.3	10,805	50.0	332	23.2
Liposomal Amphotericin B	6,302	27.3	5,524	25.5	778	54.4
Amphotericin B	2,204	9.5	2,043	9.4	161	11.2
Others / Not used[4]	1,784	7.7	1,703	7.9	81	5.6
Missing[3]	1,598	6.9	1,521	7.0	77	5.3

Treatment for failure	**N**	**%**	**N**	**%**	**N**	**%**
Liposomal Amphotericin B	718	3.1	686	3,2	32	2,2
Amphotericin B	567	2.4	538	2,5	29	2,0
Other[4]	233	1.0	230	1,0	3	0,2
Not applicable	7,841	34.0	7629	35,3	212	14,8
Outcome	**N**	**%**	**N**	**%**	**N**	**%**
Cure	15,907	69,1	14,906	69.0	1,001	70,0
Death from other causes	588	2,55	548	2,5	40	2,8
Death from VL	175	7,6	1,668	7,7	82	5,7
Transfer	1,251	5,4	1,178	5,4	73	5,1
Abandonment	180	0,78	157	0,7	23	1,6
Missing	4,924	14,6	3,139	14,5	210	14,7

[1]n (%)

[2]Pearson's Chi-squared test

[3]Was not considered a test category

[4]Pentamidine, miltefosine and drug association

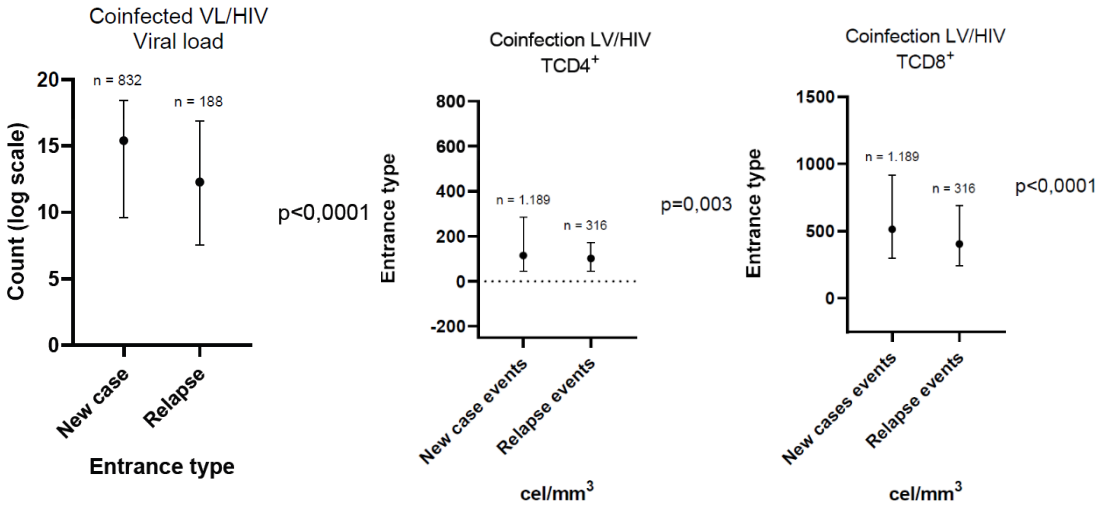
After excluding cases classified as transfer or with missing outcome, the cure rate was 87.1% among new cases and 89.1% among relapse cases (p = 0.048). The case fatality rate due to visceral leishmaniasis was 9.7% among new cases and 7.3% among relapse cases (p = 0.008). Deaths from other causes were 548 (3.2%) among new cases and 40 (3.6%) among relapse cases. The overall case fatality rate was 12.9% among new cases and 10.9% among relapse cases (p = 0.048). Treatment abandonment was 0.9% among new cases and 2.0% among relapse cases (Table 3).

Regardless of the type of entry, the values for treatment opportunity, defined as the difference between the treatment date and the date of symptom onset, did not exhibit significant difference between new case and relapse events. In both, the median treatment opportunity was 30 days (interquartile range [IQR], 1–31 days) (p=0,9).

Treatment opportunity was also calculated based on the difference between the treatment date and the notification date. In this case, we see that the median was zero days, and this finding should be interpreted with caution.

For the laboratory variables (TCD4+ and TCD8+ lymphocyte counts, as well as viral load), the values whose dates were closest to the notification date of the corresponding VL episode were considered (mean of 3 months). It should be noted that the units of measurement for these variables were not specified in the databases analyzed, which limits the clinical interpretation of the absolute values but does not invalidate the statistical comparison between the groups. Statistically significant differences were observed between new cases and relapses regarding TCD4+ ($p<0.003$), TCD8+ ($p<0.0001$) and TCD4+/TCD8+ ($p<0.001$) lymphocyte counts, with lower median values among relapses when compared to new cases events. Furthermore, viral load of HIV also differed significantly between the groups ($p<0.0001$), presenting a substantially lower median among relapses compared to new cases (Figure 2).

Figure 2. TCD4+ and TCD8+ lymphocyte counts, by type of entry, in VL-HIV coinfected patients, Brazil, 2014-2020.



Supplementary Table 1 provides information on HIV treatment in patients co-infected with VL/HIV. Among new case events, there is a higher exposure to regimens such as dolutegravir (DTG) + tenofovir and lamivudine (TL) and tenofovir disoproxil fumarate, lamivudine, and efavirenz (TLE), which correspond to approximately half of the records. In contrast, among relapse entries, these

regimens are proportionally less frequent, while the "other" category represents a substantially larger portion, reaching approximately 47% of cases. Additionally, regimens based on protease inhibitors, such as atazanavir (ATV) + ritonavir (RTV) + tenofovir and lamivudine (TL), are also proportionally more frequent among relapses.

All new case events received treatment at some time during the study period, with HIV treatment initiated close to the time of VL notification, on average within 3 to 6 months, and only 0.4% received no treatment whatsoever over the study period.

Regarding the variable treatment change, a statistically significant difference was observed between new cases and relapse events ($p<0.001$). Although regimen maintenance is more frequent among new cases (31%) than among relapse events (29%), treatment changes occur more frequently in patients with relapse events, corresponding to approximately 80% of these events, compared to 69% among new case events.

Finally, the duration of HIV treatment showed a similar distribution between new cases and relapses events. Most patients are in the shortest duration category (30 months), followed by intermediate categories, maintaining comparable proportions between the groups. There was no evidence of a statistically significant difference in HIV treatment duration between relapse and new case events ($p=0.3$).

Discussion

This study explored groups of variables related to relapse events in patients with visceral leishmaniasis that have been scarcely addressed by other studies. By performing a linkage between the VL and HIV databases from SINAN, followed by linkage with the SICLOM (database management system for antiretroviral drugs) and SISCEL (database for CD4+/CD8+ and HIV viral load in HIV patients) databases, it was possible to provide a more in-depth description of relapse events in VL/HIV coinfected patients, minimize underreporting, and expand the identification of coinfected individuals.

Although HIV testing is recommended for all VL cases, differences in the classification of 'ignored' HIV status between new cases and relapses were identified. These discrepancies were only corrected through database linkage, which identified 424 new cases of VL/HIV coinfection and 40 relapse cases of VL/HIV coinfection. Even so, approximately 18.6% of registered new case events and 7.5% of relapse events still lack this information. In the recently published study, although the authors described the HIV variable, they did not explore these analyses of this specific group (Assefa et al., 2026).

We related that VL/HIV coinfection was proportionally more frequent among relapses (40.8%) when compared to new case events (10.6%), with this difference being statistically significant ($p<0.001$). The immunological impairment in coinfected VL/HIV patients was highlighted in the present study, with the median TCD4+ and TCD8+ counts being lower in relapses ($p=0.003$) than in new cases events ($p<0.001$). This fact has been extensively studied and is particularly based on lymphopenia (TCD4+), high parasite load, and high levels of cellular activation and anti-Leishmania IgG3 antibodies, which predispose these patients to relapse (Kuschnir et al., 2021; ter Horst et al., 2008).

In a cohort study conducted with patients with and without VL/HIV coinfection over a three-year period, 78.1% of coinfected VL/HIV patients relapsed and, even with remission of clinical symptoms, maintained high parasite load, hepatosplenomegaly, and pancytopenia. The immunological markers presented were failure in IFN-g secretion, low TCD4+ lymphocyte count, and high PD1 expression on both TCD4+ and TCD8+ lymphocytes (Takele et al., 2022). Furthermore, a recent study indicated alterations in the splenic white pulp of coinfected VL/HIV patients, reducing the density of splenic TCD4+ cells and the expression of genes such as IL-15, compromising the immune response against *Leishmania* spp (Fontes et al., 2024).

Another relevant point, of an operational nature, concerns the proportion of records classified as "unknown" for the "HIV" variable, comparing relapses and new cases events. This recording is substantially lower among relapses, which suggests greater diligence in completing HIV information in patients with a previous history of the disease. Thus, while the data indicates a higher prevalence of HIV coinfection among relapses, this frequency may be partially

attributable to differences in recording patterns rather than reflecting actual differences in the distribution of coinfection between the groups.

Regarding the therapeutic protocol adopted fo HIV treatment, the distribution of therapeutic regimens differed significantly between patients with new case and relapse entry types (p-value < 0.001). For relapses, regimens based on protease inhibitors, such as Atazanavir (ATV) + Ritonavir (RTV) + Tenofovir and Lamivudine (TL), were proportionally the most frequent, differing from a previous study (Costa et al., 2023). Furthermore, treatment changes occur more frequently in coinfected VL/HIV patients who relapsed, as does therapeutic failure (Cipriano et al., 2017; Van Griensven et al., 2014). It is important to note that all HIV-positive events classified as 'new cases' initiated HIV treatment, whereas 0.4% (6/1,429) of HIV-positive events classified as 'relapses' did not initiate treatment at any time during the study period. This difference may be attributable to the greater likelihood of treatment initiation associated with a recent diagnosis.

It is recommended that VL/HIV coinfected patients with a CD4+ count below 200 undergo secondary prophylaxis, aiming to reduce the episodes of relapse (Brasil, 2015; Cota et al., 2014; Lindoso et al., 2014; Maia-Elkhoury et al., 2019). Although this recommendation exists, there is no field for it in the VL case notification form, which makes it difficult to assess this variable for both new cases and relapses.

Relapse events comprise approximately 6% of visceral leishmaniasis notifications during the study period, in line with published national reports (Leite de Sousa-Gomes et al., 2017). The higher occurrence in males, both in new cases (new infections) and relapse events, was expected and has been described in previous studies (Costa et al., 2023; Santos et al., 2023). The presence of comorbidities and the lack of adherence of the male population to health services have previously been used as hypotheses to demonstrate the association of these behavioral and cultural variables with the higher frequency of illness in this group (Cloots et al., 2020). However, earlier studies have associated parasite load, a factor directly linked to disease progression, with sex hormones, particularly testosterone, in animal models (Anuradha et al., 1990). More recently, it has been demonstrated in vitro that *Leishmania (L.) infantum*

infection in macrophages derived from male cell cultures is higher than in those from females within the first 72 hours. The profile of secreted cytokines was also observed, with high levels of TNF, IL-8, and IL-10, and low levels of IL-18 and CCL2 (Bea et al., 2025).

Age is another factor associated with the quality of the immune response developed. Studies correlating leishmania parasite load with age group have indicated that extremes of age present higher parasite loads. This is likely attributable to the immaturity of the immune system in the early years of life and immunosenescence in advanced age (Bandaranayake & Shaw, 2016; Goenka & Kollmann, 2015). In the present study, the age group under 15 years concentrated the highest number of relapses events (33%), corroborating a previous study (Simão et al., 2020b). On the other hand, in the present study, the combination of the 35 to 44 years and 45 to 54 years age groups is proportionally more frequent in relapses events, representing 36% of them, whereas in new cases events they total approximately 22%. This pattern suggests that relapses tend to occur more frequently in adults, while new cases are relatively more concentrated in younger age groups. It is also noteworthy that this is the sexually active age group, which has the highest proportion of VL/HIV coinfected patients (Freire et al., 2023; Leite de Sousa-Gomes et al., 2017; Simão et al., 2020b).

Education level is not a mandatory field in SINAN notifications. As a result, more than half of the observations fell into the "Unknown/Not applicable" category (approximately 57% for both new cases and overall), limiting the substantive interpretation of this variable. Even so, lower education levels (up to fourth grade) were proportionally more frequent among new cases than among relapses.

In relation to diagnosis, it was observed that parasitological testing was more frequent in relapses, while serological testing was more frequent in new cases events. Parasitology is considered the method with the highest sensitivity for coinfected VL/HIV patients, as they have low antibody production. Considering that most relapses occur precisely in this population, the predominant use of parasitological testing in these events is therefore consistent (Lindoso et al., 2014; OPS, 2023).

With respect to signs and symptoms, fever, weakness, weight loss, pallor, and jaundice were significantly more frequent in new cases than in relapses

events. This pattern suggests that, at the time of notification, new cases tend to present with a more symptomatic clinical picture than relapses, although the influence of differences in the completion of the forms or in clinical follow-up between the two groups cannot be ruled out.

Hepatomegaly and, especially, splenomegaly, which in previous studies were associated with relapse events (Costa et al., 2023; Mohammed et al., 2020), had similar frequencies between the two types of entry in the present study. Although a higher frequency of clinical signs was observed in new cases events, a greater dispersion of frequencies was noted among the combinations of signs in relapse events, suggesting greater complexity in the clinical presentation and primary evaluation of patients with this type of episode. Regarding the combinations of signs and symptoms, in general, it is observed that the most frequent combinations in new cases and relapses events are quite similar, differing mainly in the relative proportions and not in the composition of the signs. The overall pattern observed in this study indicates that both new cases and relapses tend to present with multiple signs and symptoms simultaneously, reflecting complex clinical pictures at the time of notification.

About the use of medications for the treatment of VL cases, a statistically significant difference was observed by type of entry, new case or relapse. In 54% of relapse events, liposomal amphotericin B was used. These findings should be interpreted with caution, since the treatment administered does not constitute an independent causal factor for relapse, but rather a marker of clinical and epidemiological characteristics underlying the patients. One explanation may be the indication of liposomal amphotericin B recommended by the Ministry of Health (Brasil, 2014). The highest percentage of relapses occurs in coinfected VL/HIV patients (38%), a group for which liposomal amphotericin B is indicated as the first-choice drug. Other criteria are also adopted for the use of liposomal amphotericin B, notably: age (under 1 year and over 50 years), comorbidities (renal, cardiac, and hepatic insufficiency), and signs of clinical severity, which require more potent therapeutic regimens with fewer adverse effects (Brasil, 2017). In a recent systematic review that evaluated therapeutic protocols in relapse events, it was observed that, although the highest number of relapses

occurred in patients using liposomal amphotericin B, this number tended to decrease with gradual dose increases (Chhajed et al., 2024).

Differences in therapeutic failure were observed among new case and relapse events. It should be noted that the majority of records in both groups were classified as "not applicable", corresponding to 35% of new cases and 15% of relapses events, which is expected since therapeutic failure occurs only in a portion of patients undergoing treatment. The interpretation of these findings should be approached with caution, as the absolute number of events with therapeutic failure is small relative to the total database, and the analysis is strongly influenced by the large proportion of records classified as ‘not applicable’. Furthermore, although the statistical test indicates a significant difference, this significance is partially determined by the large sample size and the asymmetric distribution of categories. Therefore, the results should be interpreted descriptively and exploratory, without implying causal relationships between the type of case entry and the pattern of therapeutic failure.

The time to treatment initiation was calculated based on two references: the date of onset of signs and symptoms and the date of case notification. Considering the latter, the median was zero, which indicates that either treatment began on the same day as notification or the notification was carried out due to the need for medication release. This pattern suggests the existence of inconsistent records for this variable, possibly resulting from errors in filling out or typing dates, which reinforces the need for caution when interpreting these results. Similarly, treatment opportunity considering the date of symptom onset was also not statistically significant ($p=0.9$) between the groups, suggesting that clinical suspicion in relapse events or new cases does not differ. Treatment opportunity is closely related to patient access to health services, timely suspicion and diagnosis, and quality of care, thus avoiding unfavorable outcomes (Andrade E Silva et al., 2024; Maia-Elkhoury et al., 2019).

Deaths from visceral leishmaniasis are associated with several factors, both biological and related to access, especially linked to lack of healthcare. In the present study, deaths from VL were proportionally more frequent in new cases than in relapse events, which may reflect a lack of suspicion and delayed diagnosis in this group and, consequently, delayed therapeutic

management. On the other hand, patients who experience recurrent relapses, who are already being followed up and monitored, may receive more prompt care due to the severity of their condition and their prior history. The same is observed in coinfected VL/HIV patients, whose lethality has reduced in recent years.

This study encountered several important challenges that resulted in significant limitations. The acquisition of databases for the linkage process, despite adherence to all ethical precepts, was bureaucratic and time-consuming. Moreover, the primary limitation was the use of 'new case' and 'relapse' events as the unit of analysis instead of the individual, which limited the validation of the hypotheses, especially the evaluation of prognosis associated with relapse.

Conclusion

In the present study, several variables showed statistically significant differences between new case and relapse events. Among the factors discussed here, VL/HIV coinfection stands out, which has been extensively studied and already proven to be one of the factors most associated with relapse.

In this context, in addition to lymphopenia, variables related to the recommended therapeutic regimen for HIV (medications and treatment duration) and types of clinical signs were included in the descriptive analysis.

Authors' Contributions

Rafaella Albuquerque e Silva: Developing research question, Developing quantitative methodologies, Determining study design such as participant selection, materials, settings, data, characteristics, data collection, measurement, and analysis techniques, Ensuring the integrity, rigor and reliability of data, methods, results and resources through reviewing, verification, benchmarking, factchecking and replicating, Using data to create charts, graphs or figures, Creating the first and full version of an article.

Ana Carolina Musso: Integrating and aggregating data in diverse formats and from diverse sources. Performing statistical tests to compare different groups

within a study or evaluate change. Developing quantitative and/or qualitative methodologies and frameworks. Using data to create charts, graphs or figures.

Matheus Santos Melo: Integrating and aggregating data in diverse formats and from diverse sources. Performing statistical tests to compare different groups within a study or evaluate change. Developing quantitative and/or qualitative methodologies and frameworks. Using data to create charts, graphs or figures.

Guilherme Loureiro Werneck: Developing research question, Developing quantitative methodologies, Ensuring the integrity, rigor and reliability of data, methods, results and resources through reviewing, verification, benchmarking, factchecking and replicating, Reviewing, copy-editing, refining language and providing comments and suggestions

Gustavo Adolfo Sierra Romero: Developing research question, Developing quantitative methodologies, Determining study design such as participant selection, materials, settings, data, characteristics, data collection, measurement, and analysis techniques, Ensuring the integrity, rigor and reliability of data, methods, results and resources through reviewing, verification, benchmarking, factchecking and replicating, Reviewing, copy-editing, refining language and providing comments and suggestions

Conflict of Interest

The authors declare that they have no conflict of interest that could interfere with the impartiality of scientific work.

Data Availability Statement

The authors declare that the data used in the research are contained in the tables, figures, and supplementary file.

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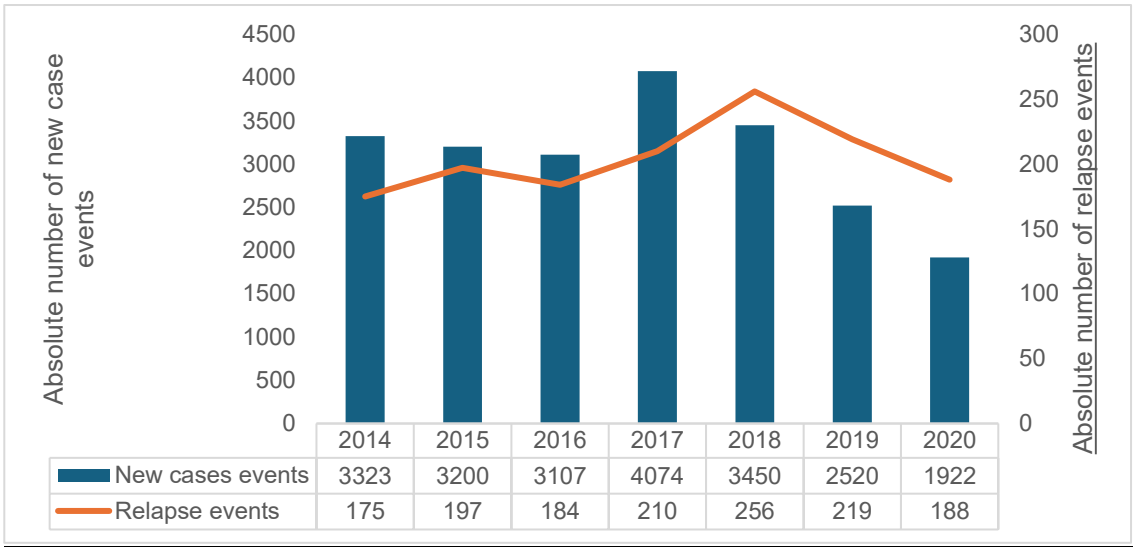
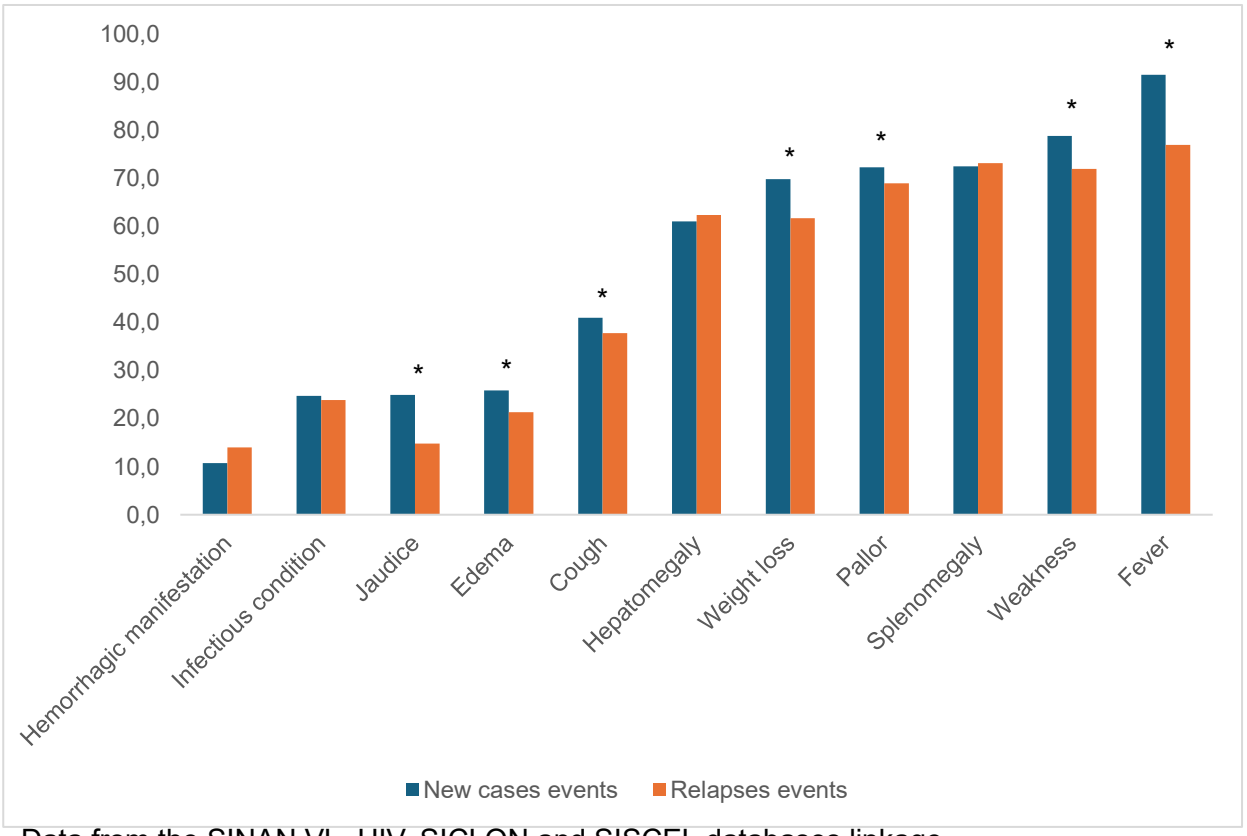
Supplementary files

Supplementary - Figure 1. New case and relapse events of VL per year, from 2014 to 2020, Brazil.



Supplementary - Figure 2. Clinical symptoms and findings in new case and relapse events of VL, from 2014 to 2020, Brazil.



Data from the SINAN VL, HIV, SICLON and SISCEL databases linkage

Supplementary - Table 1. Therapeutic ARV protocol in coinfected VL/HIV patients, by type of entry,

Brazil, 2014-2020.

Characteristic	Overall N = 2,871[1]		New cases events N = 2,293[1]		Relapse events N = 578[1]	
Antiretroviral therapy	**N**	**%**	**N**	**%**	**N**	**%**
3TC+ EFZ+ TDF	99	4.8	84	5.3	15	3.3
ATV+ RTV+ TL	193	9.4	141	8.9	52	11
AZL+ EFZ	93	4.5	79	5	14	3
DTG+ TL	486	24	431	27	55	12
LPV+ TL	74	3.6	44	2.8	30	6.5
TLE	477	23	403	25	74	16
Others	624	30	403	25	221	48
Total	2046	99.3	1585	99	461	99.8
Treatment status	**N**	**%**	**N**	**%**	**N**	**%**
Maintenance	825	29	708	31	117	20
Change	2,046	71	1,585	69	461	80
Antiretroviral therapy duration (months)	**N**	**%**	**N**	**%**	**N**	**%**
30	1604	78	1252	79	352	76
60	281	14	208	13	73	16
90	161	7,9	125	7,9	35	7,8

ATV – atazanavir; AZL - zidovudina; DTG - dolutegravir; EFV - efavirenz; LPV - lopinavir; TL – tenofovir/lamivudine; TLE - tenofovir disoproxil fumarate/lamivudine/efavirenz; 3TC - lamivudine; RTV - ritonavir

[1]n (%)

[2]Pearson's Chi-squared test; Fisher's exact test

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- The authors declare that the preparation of the manuscript followed the ethical norms of scientific communication.
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