Parasitology

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Epidemiological, clinical and laboratory aspects of human visceral leishmaniasis (HVL) associated with human immunodeficiency virus (HIV) coinfection: a *systematic review*

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Review

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Abstract

Coinfection with human visceral leishmaniasis (HVL) and human immunodeficiency virus (HIV) has become an emerging public health problem in several parts of the world, with high morbidity and mortality rates. A systematic review was carried out in the literature available in PubMed, Scielo and Lilacs related to HVL associated with HIV coinfection, seeking to analyze epidemiological, clinical and laboratory aspects. Of the 265 articles found, 15 articles were included in the qualitative analysis, which referred to the results of HVL treatment in patients coinfected with HIV. In the published articles between 2007 and 2015, 1171 cases of HVL/HIV coinfection were identified, 86% males, average age 34 years, liposomal amphotericin B was the most commonly used drug, cure rates 68 and 20% relapses and 19% deaths, five different countries, bone marrow was used in 10/15 manuscripts. HVL/HIV coinfection is a major challenge for public health, mainly due to the difficulty in establishing an accurate diagnosis, low response to treatment with high relapse rates and evolution to death. In addition, these two pathogens act concomitantly for the depletion of the immune system, contributing to worsening the clinical picture of these diseases, which requires effective surveillance and epidemiological control measures.

Introduction

Geographic overlap of human visceral leishmaniasis (HVL) associated with acquired human immunodeficiency virus (HIV) infection is an emerging public health problem with high mortality rates in 35 countries, according to the World Health Organization (WHO). Most cases of HVL/HIV coinfection occur in Spain, France, Italy and Portugal (de Albuquerque *et al.*, 2014; Martins-Melo *et al.*, 2014), with 71.1% of cases being observed in drug users (Ministério da Saúde, 2015), among whom the transmission of amastigotes forms of *Leishmania* occurs through contaminated needles (Marques *et al.*, 2007; Van Griensven *et al.*, 2014*a*). High rates of coinfection were also recorded in developing countries, such as Brazil (Lindoso *et al.*, 2014; Távora *et al.*, 2015) and Índia (Burza *et al.*, 2014*b*; Mahajan *et al.*, 2015), and underdeveloped countries, such as Ethiopia (Ritmeijer *et al.*, 2011; Diro *et al.*, 2015). The data show that coinfection occurs mainly in the age group close to 38 years of age, in males (91.6%) and homosexuals (de Souza *et al.*, 2012*b*; Silva *et al.*, 2013). However, there has been an increase in heterosexuals and women (Nascimento *et al.*, 2011; Coura-Vital *et al.*, 2014). Coinfection has also been found in non-endemic countries for HVL, as in North America (Távora *et al.*, 2015).

Clinical manifestations of HVL/HIV coinfection are similar in patients with HVL, who present fever, cough, weight loss, bleeding, oedema, cutaneous pallor and hepatosplenomegaly (Távora *et al.*, 2015; Fontoura *et al.*, 2016), except for the presence of diarrhoea, more frequent in coinfected patients (Lima *et al.*, 2013; de Albuquerque *et al.*, 2014). Coinfection can be fatal if not diagnosed and treated properly in a timely manner. In HVL/HIV, it may be more aggressive or may not present clinical signs characteristic of HVL, such as hepatosplenomegaly (Dupnik *et al.*, 2011), making the diagnosis more difficult (de Almeida e Cavalcanti *et al.*, 2012; Abass *et al.*, 2015), since clinical manifestations are similar to other diseases (Cota *et al.*, 2013*b*). Parasitological examination of bone marrow is the gold standard diagnostic test for HVL in people with HIV (Silva *et al.*, 2013; Costa *et al.*, 2013*b*).

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HVL/HIV treatment is still a major challenge, considering: low therapeutic efficacy, high frequency of adverse reactions, relapses, deaths (Craft *et al.*, 2010; Cota *et al.*, 2014) and resistance of pathogens to medications (Inocêncio *et al.*, 2011; Santos-Oliveira *et al.*, 2013). Therapy and prophylaxis recommended by the WHO are liposomal amphotericin B (Lindoso *et al.*, 2014; Ministério da Saúde, 2015; Távora *et al.*, 2015). Clinical cure is established when haematological parameters normalize and there is remission of hepatosplenomegaly and fever (Cota *et al.*, 2014). The patient should be followed up indefinitely (Ministério da Saúde, 2015). Treatment efficacy and low occurrence of relapses may also be linked to the use of highly active antiretroviral therapy (HAART) (Dupnik *et al.*, 2011; Lima *et al.*, 2013).

Despite the epidemiological impact and clinical implications of HLV/HIV coinfection, few randomized studies are available that include epidemiological data, diagnosis, treatment, follow-up (relapses, cure and death), control, data on $CD4^+$ T cell counts, HAART, laboratory tests and clinical manifestations. The objective of this study was to perform a systematic review of the literature found in PubMed, Sciello and Lillacs, evaluating epidemiological, clinical and laboratory aspects in the context of treatment of HVL/HIV coinfection.

Methods

A systematic review was carried out through bibliographic research available in PubMed, Scielo and Lilacs according to the Mesh descriptors available (https://www.ncbi.nim.nih.gov/mesh), 'human visceral leishmaniasis ', 'HIV coinfection', 'epidemiology', 'treatment', 'diagnosis', 'symptoms', 'mortality' and 'control' (Fig. 1). Considering the inclusion and exclusion criteria (Fig. 2), we selected articles published in the last 10 years.

We found 238 articles in PUBMED, 16 in Scielo and nine in Lillacs, in a total of 265 articles. We excluded 195 articles by title and/or abstract and for having a different scope from the chosen subject. Of these, 70 articles were submitted to the eligibility analysis, read in full and data were extracted by one author (I.G.F.) and verified by another author (A.L.A.S.). Methodological recommendations were followed according to PRISMA guidelines that is a checklist containing a minimum set of items based on evidence for systematic reviews and meta-analysis reports as a basis for report reviews other types of research systematic, mostly interventive reviews (Table A in S1 Text) (Galvão *et al.*, 2015; Shamseer *et al.*, 2015) for systematic reviews and, according to guidelines, they were registered in PROSPERO (http://www.crd.york.ac.uk/prospero/searchadvanced.php) on 16 October 2016 (registration number: 42016049586) to help to minimize the risk of bias (Shamseer *et al.*, 2015). Authors were contacted by e-mail in order to obtain more information on primary data and on aspects of the studies more clearly, such as the full description of the treatment with respect to the first and the second therapy with the therapeutic regimen, prophylaxis, follow-up (cure, relapses/recurrences, abandonment and deaths), time of diagnosis of HVL in relation to the diagnosis of HIV, use of HAART and mainly statistics that were made referring to the data surveyed, but that were not described in the articles (Shamseer *et al.*, 2015).

Fifteen studies were included for qualitative synthesis and 55 articles were excluded because they did not present treatment data or were incomplete.

The included studies have satisfactorily answered the research question: what does the current literature tell us about epidemiology, treatment, diagnosis, symptoms, mortality and control of HVL/HIV coinfection in different parts of the world?

We included all the articles whose main topic was the treatment of HIV/HVL coinfection, regardless of study design. Regarding the participants, we included patients with HIV that were coinfected with HVL, as reported in the studies. We excluded studies with a mixed population (HVL and HVL/HIV) that did not specify the coinfected group by HIV and leishmaniasis or that did not specify the treatment. Article selection was carried out by two reviewers (I.G.F., A.L.A.S.), after reaching a consensus between both or a third party (D.S.B.).

The characteristics of the studies were detailed considering the author's identification, year of publication, country and place of study, number of HIV/HVL coinfected cases, study period, gender, age, study design, therapy, follow-up (cure, period, relapse, abandonment or loss, death), HAART, $CD4^+$ cell count, clinical manifestations cited by three or more authors, time of diagnosis, diagnostic methods cited by three or more authors and use of antiretrovirals. There was no restriction by language.

We also aimed to show the relationship and results between and among the included studies, presented throughout the text and in tables, explaining the data and their characteristics referring to the epidemiological, clinical, laboratory and treatment aspects of LV/HIV coinfection (Whitehead *et al.*, 2013).

The guidelines and norms outlined by PRISMA checklist for systematic reviews were followed. Due to incompleteness of the data and heterogeneity of the information found, it was not possible to perform meta-analysis, since the odds ratio (OR) or hazard ratio (HR), performed in four studies, was not done with the same variables, as gender, years of study, therapy and follow-up (de Albuquerque *et al.*, 2014); HR for therapy, exams and clinical manifestations (de Souza *et al.*, 2012*a*); OR for concomitant diseases, exams, clinical manifestations and methods of examination (Hurissa *et al.*, 2010); and OR for the time of diagnosis (Cota *et al.*, 2014).

Results

Fifteen original articles were selected for qualitative synthesis, involving studies in five different countries (Table 1). Most of them (six) were conducted in Brazil (ID: 1, 2, 3, 4, 5, 6), four

("leishmaniasis, visceral"[MeSH Terms] OR ("leishmaniasis"[All Fields] AND "visceral"[All Fields]) OR "visceral leishmaniasis"[All Fields] OR ("visceral"[All Fields] AND "leishmaniasis"[All Fields])) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("coinfection"[MeSH Terms] OR "coinfection"[All Fields] OR ("co"[All Fields] AND "infection"[All Fields]) OR "co infection"[All Fields]) AND (epidemiology OR therapy OR treatment OR therapeutics OR diagnosis OR symptoms OR mortality prevention and control OR prevention OR "control OR control groups OR groups)

Fig. 1. Terms used for search in PUBMED, SCIELO and LILACS.

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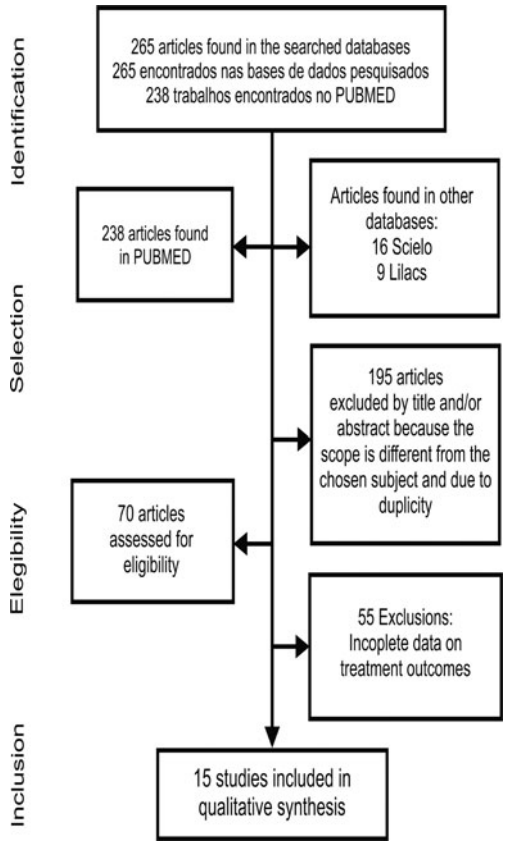

Fig. 2. PRISMA flowchart of inclusion and exclusion of articles for the review.

in Ethiopia (ID: 8, 12, 13, 15), three in India (ID: 7, 9, 11), one in Spain (ID: 14) and in France (ID: 10). Thirteen studies were conducted in developing countries and two in developed countries (ID: 10, 14). Regarding the patients, 1171 cases of HVL/HIV coinfection were identified in a 20-year study period, from 1994 to 2014. In only two articles the time period of the study was longer, with 9 (ID: 10) and 16 years (ID: 4); the others were evaluated in periods ranging from 2 to 6 years. Regarding the study design, there were five descriptive (case series) and ten analytical (cohort). Regarding sample size, seven studies had between 15 and 50 subjects, four from 50 to 100 participants, and four had more than 100 patients.

Table 1. Characteristics of the study HVL/HIV coinfection, last 10 years

Characteristics	*N*	%
Year of study		
2010 onwards	5	33
2007–2012	1	7
1994–2010	9	60
Study design		
Descriptive – case series	5	33
Analytical – cohort	10	67
Location		
Africa	4 (4-Ethiopia)	27
Americas	6 (6-Brazil)	40
Southeast Asia	3 (3-India)	20
Europe	2 (1-Spain, 1-France)	13
Sample size		
15–50	7	46
50–100	4	27
More than 100	4	27

N, number.

Most of the patients were male 86% male (1007 out 1171 patients). Regarding age group, the median and median age was around 34 years (Table 2).

With regard to study designs (Table 3), most were prospective cohort (ID: 3, 10, 12, 14) and retrospective studies (ID: 1, 5, 7, 8, 9, 11, 13, 15). The other articles were descriptive (ID: 2, 6), retrospective and prospective studies (ID: 4).

Different treatment regimens were compared considering the 15 HVL/HIV coinfection studies encompassing 1171 patients treated. The most commonly used drug was liposomal amphotericin B (Table 3) both in dual therapy regimens and in monotherapy. In studies performed with only one group of individuals, we found one therapeutic regimen used in three studies, the liposomal amphotericin B (ID: 7, 11, 14), and other two studies with therapeutic regimens using amphotericin B and pentavalent antimony (Sb^v) (ID: 6, 10). The other studies reported the use of different therapeutic regimens, (Sb^v), amphotericin B and liposomal amphotericin B (ID: 4), sodium stibogluconate (ID: 8), liposomal amphotericin B and miltefosine (ID: 9), sodium stibogluconate, liposomal amphotericin B, miltefosine and paromomycin (ID: 12). In the six studies performed in two groups of patients, they compared different therapeutic regimens, (Sb^v), amphotericin B and liposomal amphotericin B (ID: 2, 3), amphotericin B and (Sb^v) (ID: 1, 5), (Sb^v) and liposomal amphotericin B (ID: 13) and liposomal amphotericin B (ID: 15), which is the most commonly used drug in both dual therapy and monotherapy regimens. Due to the diversity in the therapeutic regimens, it was not possible to carry out the direct comparison between studies. The cure was obtained in 68% (781/1147) of cases, recurrence in 20% (231/1140) and 19% (132/707) of deaths.

The dose of the therapeutic regimen was specified in 60% of the included studies. From 15 selected studies, ten specified a change of treatment for a second leishmanicidal therapy, where liposomal amphotericin B was mostly used and the first-choice treatment regimen was sbv or even L-Amb. Only five studies described the medication dosage (ID: 1, 6, 8, 12, 15) and the prophylactic regimen to avoid relapses during follow-up (ID: 3, 10, 12, 13).

In four studies, the monotherapy regimen by L-Amb was mostly used, where an average between the 66% cure percentages, with 10% deaths, despite the high relapses percentage of 23% (ID: 7, 11, 14, 15). However, therapeutic regimens combined with sb^v, both with AMB (ID: 2, 4, 5, 6) and L-Amb (ID: 13), the mean death percentage was 17%, even with the mean cure percentage similar to the monoterapy L-Amb regimen and relapses percentage of 17 and 14, respectively. However, the highest relapses percentage, 30%, was found in a study with combined therapy between AMB and L-Amb; however, the death percentage was 9%. However, the study with a greater percentage (12%) of losses during follow-up was in a combined regimen with L-Amb, SSG, and miltefosine, with 7% of deaths (ID: 12).

Data on the treatment and follow-up of HVL/HIV coinfected patients (Table 4) show the sequence of years of the studies, the number of cases, the percentage of patients who used the drugs and had their cure, relapses or failures and deaths. During the 20-year period, 1171 patients were treated; of these, considering relapse or lack of data in some articles, abandonment or loss during follow-up, 781 (68%) were cured, 231 (20%) suffered relapses or failures and 182 (16%) died. Of the patients who evolved to death, only eight studies specified the reasons for the deaths

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Table 2. Epidemiological characteristics

ID number	Author (year of publication), study location	Study period	No. of cases	A – N°. (%)	F – N°. (%)	Min–Max	No. (%)	A ± S.D., A or M (IQR)
9	Mahajan *et al.* (2015); Bihar, India	2012–2014	102	77 (76)	25 (24)	<15	2 (2.0)	36 (30.45)[a]
						15–29	13 (12.7)	
						30–44	58 (56.9)	
						>60	6 (5.9)	
12	Diro *et al.* (2015); Gondar and Abdurafi, Ethiopia	2011–2013	74	71 (96)	3 (4)	N/F	N/F	32 (28–37)[a]
8	Diro *et al.* (2014*a*, 2014*b*); Northwest Region, Ethiopia	2011–2013	57	56 (98.2)	1 (1.8)	28–36	N/F	32 (28–35)[a]
3	Cota *et al.* (2014); Belo Horizonte, Minas Gerais, Brazil	2011–2013	46	38 (83)	8 (17)	N/F	N/F	41.0 ± 10.9[b]
1	Távora *et al.* (2015); Ceará, Brazil	2010–2012	42	37 (88.1)	5 (11.9)	18–35	N/F	35 ± 9.2[b]
7	Burza *et al.* (2014*a*, 2014*b*); Bihar, India	2007–2012	159	132 (83.0)	27 (17)	<14	5 (3.1)	N/F
						14–25	4 (2.5)	
						25–35	49 (30.8)	
						35–45	64 (40.3)	
						45–55	27 (17.0)	
						>55	10 (6.3)	
2	de Albuquerque *et al.* (2014); Tocantins, Brazil	2007–2010	33	26 (78.8)	7 (21.2)	0–10	8 (24.2)	27.9 ± 15.1[b]
						11–17	0 (0)	
						18–50	24 (72.7)	
						>50	1 (3)	
11	Sinha *et al.* (2011); Bihar, India	2007–2010	55	46 (83.6)	9 (16.4)	<15	2 (3.6)	35 (30–40)[a]
						30–40		
15	Ritmeijer *et al.* (2011); Humera and Abdurafi, Ethiopia	2007–2009	195	179 (91.8)	16 (8.2)	N/F	N/F	30 (10–56)[a]
13	Hurissa *et al.* (2010); Gondar and Kahsay Abera, Ethiopia	2006–2008	92	87 (94.6)	5 (5.4)	18–55	N/F	32.2 ± 7.0[b]
14	Molina *et al.* (2007); Barcelona, Spain	2001–2005	15	14 (93)	1 (7)	N/F	N/F	36 (26–53)[a]
6	Alexandrino-de-Oliveira *et al.* (2010); State of Mato Grosso do Sul, Brazil	2000–2006	23	20 (87)	3 (13)	20–40	16	37[c]
						41–60	7	
						21–56		
5	de Souza *et al.* (2012*a*, 2012*b*); Belo Horizonte, Minas Gerais, Brazil	2000–2005	27	22 (81.5)	5 (18.5)	N/F	N/F	37.6 ± 10.9[b]
10	Bourgeois *et al.* (2008); Montpellier and Nimes, France	1995–2004	27	22 (81.5)	5 (18.5)	30–51	N/F	35[c]

4	Lima *et al.* (2013); Teresina, Piauí, Brazil	1994–2010	224	185 (83.2)	39 (16.8)	3m-11y	9 (4)	3.6[c]		
						20–40	143(63.9)	N/F		
	Total		1171	1012 (86)	159 (14)			34.1[b]		
	Brazil – 6 (39)							34.4[a]		
	India – 3 (20)									
	Ethiopia – 4 (27)									
	Spain – 1 (7)									
	France – 1 (7)									

No. (%), number of cases and percentage; N/F, not found; 'ID' number (identifier for each included paper).
[a]M (IQR): median and interquartile range.
[b]A ± s.d.: average and standard deviation.
[c]A: average.

(ID: 1, 2, 6, 10, 11, 12, 14, 15). Of these, 11 (6%) occurred as a consequence of HVL, 39 (21%) were due to complications of HIV or other concomitant infections, and 132 (73%) did not specify the reasons for deaths.

Due to the small number of studies and their heterogeneity, it was not possible to compare the therapeutic regimens. However, our data suggest that there is a better tolerance in coinfected patients with LV/HIV, by the liposomal amphotericin B (L-Amb) compared to pentavalent antimony or conventional amphotericin B, which favours clinical efficacy.

Treatment efficacy was evaluated based on remission of signs and symptoms of HVL, improvement of haematological parameters and absence of recurrence after the follow-up period (ID: 1, 3, 6, 7, 8, 9, 10, 11, 13, 14, 15). Of the ten studies that reported follow-up, seven reported follow-up for 12 months or more after treatment (ID: 1, 7, 9, 10, 11, 12, 14), 2 followed patients up to 6 months (ID: 8, 13) and one reported having performed three evaluations (1st, 2nd and 6th month) (ID: 15). Seven articles refer to the loss of patient's location or abandonment of treatment, 3% (21/655) during follow-up (ID: 7, 8, 9, 11, 14, 15).

Among the clinical manifestations (Table 5), we selected the ten most mentioned, in sequence. The most cited was anaemia and/or cutaneous pallor (12/15 studies; 589/923; 64% of patients) (ID: 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14); splenomegaly (11/15; 698/911; 77%) (ID: 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13); fever (9/15; 87%) (ID: 1, 2, 3, 4, 5, 6, 11, 13, 14); weight loss (9/15; 479/660; 73%) (ID: 1, 2, 3, 4, 6, 9, 11, 12, 13); hepatomegaly (8/15; 53%) (ID: 1, 2, 3, 4, 5, 6, 9, 12); cough (6/15; 265/504; 53%) (ID: 1, 2, 4, 5, 11, 13); diarrhoea (6/15; 39%) (ID: 1, 3, 4, 5, 12, 13); bleeding (6/15; 127/496; 26%) (ID: 1, 2, 3, 4, 5, 13); astenia (5/15; 364/477; 76%) (ID: 1, 2, 4, 11, 13) and jaundice (4/15; 68/362; 19%) (ID: 2, 3, 4, 5).

All the Brazilian studies included in this review described most of the symptoms, unlike studies in other countries included in this review, and a study from Ethiopia and France that did not report on signs and symptoms of VL/HIV. Among the symptoms most cited in the studies in Brazil, in descending order, there were fever, skin paleness and/or anemia, weight loss, splenomegaly, asthenia, hepatomegaly, cough, diarrhoea, bleeding and jaundice. In the countries of Ethiopia and India, the most frequently mentioned symptoms in descending order were splenomegaly, skin paleness and/or anaemia, weight loss, asthenia, hepatomegaly, fever, cough, diarrhoea and bleeding.

The classical triad of fever, anaemia, and splenomegaly was similar to studies in Brazil, except for weight loss, more frequent than splenomegaly. However, splenomegaly was more commonly found in studies in Ethiopia and India, followed by skin paleness and/or anaemia and weight loss.

Regarding the diagnostic method, the articles showed that parasitological examination was the most used in 69% of the analyses (Table 6), cited by ten studies (771/1117) (ID: 1, 4, 6, 7, 8, 9, 10, 11, 13, 14), that parasitological exam of bone marrow aspirates is the gold standard diagnostic test. In three other studies, the culture was carried out to isolate the parasite (ID: 4, 6, 10). There are also reports of material collection or aspiration puncture for parasitological examination of the liver (ID: 9) and spleen (ID: 9, 8, 13). Serological tests were less frequent in only 31% of the tests (346/1117), cited in seven studies, and in two articles the authors did not specify the type of test (ID: 3, 13), in which the recombinant rapid antigen test (RK39) was the most commonly used, mentioned in 5/15 studies (164/405; 40%) (ID: 1, 9, 7, 11, 13), and the indirect immunofluorescence test (IFAT) in 1/15 study (113/150; 75%) (ID: 4). The polymerase chain reaction (PCR) test was mentioned only by one study (27/27; 100%) (ID: 10).

The parasitological exam is considered the gold standard diagnostic test in coinfection HVL/HIV to *Leishmania* amastigotes detection in spleen, liver and bone marrow. However, in the

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Table 3. Treatment recommendations for HVL/HIV

			Used medications							
			1st therapy			2nd therapy			Profilaxia	
ID number	Author (year)	Type of study	Leishmanicide	*N* (%)	Posology	Leishmanicide	*N* (%)	Reason for change	Therapeutic regimen	
1	Távora *et al.* (2015)	Cohort retrosp. 2 groups, Comparison result: favourable and unfavourable	AMB	37/41 (97)	N/F	L-AmB	11/41 (27)	Adverse events		
			Sb^v	1/41 (3)		AMB	1/41 (2.5)	Diagnosis of HIV+	N/F	
2	de Albuquerque *et al.* (2014)	Desc. study. 2 groups, comparative: VL and VL/HIV	Sb^v	20/33 (63)	N/F	N/F	N/F	N/F	N/F	
			AMB	7/33 (22)						
			L-AmB	3/33 (9)						
			Did no use	2 (6)						
3	Cota *et al.* (2014)	Cohort prosp. 2 groups, comparative: VL and VL/HIV	Sb^v	1/46 (2)	20 mg kg^{-1}/d.	L-AmB	N/F	Severity toxicity	L-AmB2X/month $CD4^+$ <350 cells	
			AMB	28/46 (61)	N/F	Sb^v	N/F	Kidney problems		
						L-AmB	N/F			
			L-AmB	17/46 (37)		No change	–			
			Commuta	11/46 (24)						
4	Lima *et al.* (2013)	Re-prosp. study. 1 group, diagnosis and treatment	Sb^v	117/224 (45.7)	N/F	N/F	N/F	N/F	N/F	
			AMB	142/224 (55.5)	N/F					
			L-AmB	14/224 (5.5)	N/F					
5	de Souza *et al.* (2012*a*, 2012*b*)	Cohort retrosp. 2 groups, comparative: VL and VL/HIV	Sb^v	23/27 (85)	N/F	AMB	N/F	Adverse reactions	N/F	
			AMB	4/27(15)	N/F					
6	Alexandrino-de-Oliveira *et al.* (2010)	Desc. study. 1 group, review of medical records	Sb^v	17/23 (74)	20 mg kg^{-1}/30 d.	AMB	12/17 (71)	Adverse reactions	N/F	
			AMB	4/23 (17)	0.7–1 mg kg^{-1}/28 d.			Amylase >		
			Did no use	2/23 (9)						
7	Burza *et al.* (2014*a*, 2014*b*)	Cohort retrosp. 1 group, observational	L-AmB	150/159 (94.3)	20 mg kg^{-1}	There was no change	N/F	N/F	N/F	
			Have already treated w/L-AmB 20 mg kg^{-1}	8/159 (5)	25 mg kg^{-1}					
8	Diro *et al.* (2014*a*, 2014*b*)	Cohort retrosp. 1 group, diagnosis and treatment	SSG	57/57 (100)	20 mg kg^{-1} during 30 d.	L-AmB	2/18	Intolerance, failure, kidney, pancreas problems	N/F	
						SSG (repated)	14/18			
						L-AmB and miltefosine	2/18			
9	Mahajan *et al.* (2015)	Cohort retrosp. 1 group, diagnosis and treatment	L-AmB (AmBisome)	102/102 (100)	30 mg kg^{-1} 6×/d.	N/F	N/F	N/F	N/F	
			X Miltefosine	102/102 (100)	⩾25 kg/50 mg b.i.d.; 12–<25 kg/50 mg q.d. 14 d.					

10	Bourgeois *et al.* (2008)	Cohort prosp. 1 group, recurrence follow-up	Sb^v	1/27 (3.7)	N/F	N/F	N/F	N/F	27(100) AMB ou L-AmB
			AMB	26/27 (96.3)	0.8–1 g				
11	Sinha *et al.* (2011)	Cohort retrosp. 1 group, comparative (before and after)	L-AmB (AmBisome)	50/55 (90.9)	20 mg kg^{-1} –4×	N/F	N/F	N/F	N/F
				5/55 (9.1)	25 mg kg^{-1} – 5×				
12	Diro *et al.* (2015)	Cohort prosp. 1 group, treated recurrences	SSG	38/74 (28)	N/F	SSG	18 (51.4)	11/74 (14.9)	Pentamidine 4 mg kg^{-1} (Up to 300 mg)
			L-AmB	49/74 (35)	N/F	L-AmB	25 (71.4)		
			Miltefosine	41/74 (30)	N/F	Miltefosine	22 (62.9)		
			Paromomycin	9/74 (7)	N/F	Paromomycin	5 (14.3)		
13	Hurissa *et al.* (2010)	Retrosp. study. 2 groups, comparative: VL and VL/HIV	Sb^v	53/92 (57.6)	20 mg kg^{-1}, 28–30 d.	L-AmB (AmBisome)	N/F	N/F	AMB 1X month
			L-AmB	39/92(42.4)	N/F	N/F	N/F		
14	Molina *et al.* (2007)	Prosp. study 1 group, reinfection or recurrence	L-AmB	15/15 (100)	4 mg kg^{-1} d^{-1}. 5 d., then, once a week. 5 weeks (10 × 40 mg kg^{-1})	L-AmB	N/F	N/F	N/F
15	Ritmeijer *et al.* (2011)	Cohort retrosp. 2 groups, risk factors for treatment failure	L-AmB (AmBisome)	195/195 (100)	25 and 40.5 mg kg^{-1} (A of 30.0 mg kg^{-1})	L-AmB	5/63 (8)	Parasitological insufficiency	N/F
						SSG	58/63(92)		
	Total 15	Cohort: 10	Sb^v	233/513 (45)	9/15 (60) specified	Sb^v: 1	5/15 = 175/213 (82)	6/15	4/15
		Prosp. studies.: 4	AMB	248/421 (59)		SSG: 3			AMB or L-AmB = 1
		Retrosp.: 8	L-AmB	642/995 (65)		AMB: 3			AmB = 1
		Pro-retrosp.: 1	SSG	95/131 (73)		L-AmB			or L-AmB = 1
		Desc.: 2	Miltefosine	143/176 (81)		10/15 specified			Pentamidine = 1
		1 group: 9	Paromomycin	9/74 (12)					
		2 groups: 6	Total (%)	1370/1171					

Sb^v, pentavalent antimony; AMB, Amphotericin B deoxycholate; L-AmB, liposomal Amphotericin B; SSG, sodium stibogluconate; d., days; Retrosp., retrospective; Prosp., prospective; Desc., descriptive; q.d., once a day; b.i.d., twice a day; mg kg^{-1}, milligrams/kilogram; A, average; –/–, number of events and total value; 'ID' number (identifier for each included paper).

Table 4. Data on the number of cases per study and percentages of treatment, cure, relapses/recurrences and deaths

Author (Year)	Lima *et al.* (2013)	Bourgeois *et al.* (2008)	de Souza *et al.* (2012*a*, 2012*b*)	Alexandrino-de-Oliveira *et al.* (2010)	Molina *et al.* (2007)	Hurissa *et al.* (2010)	Ritmeijer *et al.* (2011)	Sinha *et al.* (2011)	de Albuquerque *et al.* (2014)	Burza *et al.* (2014*a*, 2014*b*)	Távora *et al.* (2015)	Cota *et al.* (2014)	Diro *et al.* (2014*a*, 2014*b*)	Diro *et al.* (2015)	Mahajan *et al.* (2015)
ID number	4	10	5	6	14	13	15	11	2	7	1	3	8	12	9
Study period	1994–2010	1995–2004	2000–2005	2000–2006	2001–2005	2006–2008	2007–2009	2007–2010	2007–2010	2007–2012	2010–2012	2011–2013	2011–2013	2011–2013	2012–2014
Number of cases	224	27	27	23	21	92	195	55	33	159	42	46	57	74	102
Sb^v (%)	46	4	85	74	0	58	0	0	63	0	3	2	0	0	0
AMB (%)	56	96	15	17	0	0	0	0	22	0	97	61	0	0	0
L-Amb (%)	6	0	0	0	100	42	100	100	9	100	0	37	0	35	100
SSG (%)	0	0	0	0	0	0	0	0	0	0	0	0	100	28	0
Miltefosine (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	30	100
Paromomycin (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	7	
Cure	71	41	78	43	71	68	59	75	73	58	72	61	75	61	75
Relapse, failure (%)	10	33	0	48	29	14	32	15	9	16	21	30	5	20	6
Death (%)	19	26	22	9	0	17	7	11	18	23	7	9	16	7	18
Lost to follow-up (%)	0	0	0	0	0	0	2	0	0	4	0	0	4	12	1

Percentage averages	ID number	Cure	Relapse, failure (%)	Death (%)	Lost to follow-up (%)
AMB (%)	10, 1	57	27	17	0
L-Amb (%)	7, 11, 14, 15	66	23	10	2
AMB/L-Amb (%)	3	61	30	9	0
Sb^v/AMB (%)	2, 4, 5, 6	66	17	17	0
Sb^v/L-Amb (%)	13	69	14	17	0
L-Amb/miltefosine (%)	9	75	6	18	1
SSG (%)	8	75	5	16	4
L-Amb/SSG/miltefosine (%)	12	61	20	7	12

Sb^v, pentavalent antimony; AMB, amphotericin B deoxycholate; L-AmB, liposomal Amphotericin B; SSG, sodium stibogluconate; (%), percentage; 'ID' number (identifier for each included paper).

Table 5. Main clinical manifestations of patients with VL/HIV coinfection

ID number	Author (year)	Cough *n* (%)	Weight loss, *n* (%)	Bçeeding, *n* (%)	Diarrhoea, *n* (%)	Fever, *n* (%)	Hepatomegaly, *n* (%)	Splenomegaly, *n* (%)	Astenia, *n* (%)	Pallor and/or anaemia, *n* (%)	Jaundice, *n* (%)
1	Távora *et al.* (2015)	21/42 (50)	38/42 (90)	6/42 (14)	21/42 (50)	39/42 (92)	33/42 (78)	32/42 (77)	33/42 (79)	26/42 (63.4)	N/F
2	de Albuquerque *et al.* (2014)	17/33 (51.5)	25/33 (75.8)	0/33 (0)	N/F	31/33 (93.9)	17/33 (51.5)	20/33 (60.6)	28/33 (84.8)	22/33 (66.7)	9/33 (27.3)
3	Cota *et al.* (2014)	N/F	28/46 (60.9)	9/46 (19.6)	10/46 (21.7)	28/46 (60.9)	31/46 (67.4)	31/46 (67.4)	N/F	4/46 (8.7)	7/46 (15.2)
4	Lima *et al.* (2013)	135/256 (52.7)	202/256 (78.9)	76/256 (29.7)	107/224 (41.8)	220/256 (85.9)	109/256 (42.6)	165/256 (64.4)	203/256 (79.3)	234/256 (91.4)	46/256 (17.9)
5	de Souza *et al.* (2012*a*, 2012*b*)	18/27 (66.7)	N/F	7/27 (25.9)	11/27 (40.7)	24/27 (88.9)	21/27 (77.8)	21/27 (77.8)	N/F	26/27	6/27 (22.2)
6	Alexandrino-de-Oliveira *et al.* (2010)	N/F	9/23 (39)	N/F	N/F	23/23 (100)	18/23 (78)	18/23 (78)	N/F	16/20 (80)	N/F
7	Burza *et al.* (2014*a*, 2014*b*)	N/F	N/F	N/F	N/F	N/F	N/F	139/159	N/F	80/159	N/F
8	Diro *et al.* (2014*a*, 2014*b*)	N/F	N/F	N/F	N/F	N/F	N/F	54/57 (94.7)	N/F	55/57 (96)	N/F
9	Mahajan *et al.* (2015)	N/F	29/40 (71.6)	N/F	N/F	N/F	63/102 (61.8)	96/102 (94.1)	N/F	48/102 (47)	N/F
10	Bourgeois *et al.* (2008)	N/F		N/F	N/F	N/F	N/F	N/F	N/F	N/F	N/F
11	Sinha *et al.* (2011)	15/54 (27.8)	7/54 (13.0)	N/F	N/F	54/54 (100)	N/F	N/F	8/54 (14.8)	N/F	N/F
12	Diro *et al.* (2015)	N/F	56/74 (76)	N/F	24/74 (68)	N/F	29/74 (39)	30/74 (41)	N/F	7/74 (9)	N/F
13	Hurissa *et al.* (2010)	59/92 (64.1)	85/92 (92.4)	29/92 (31.5)	38/92 (41.3)	88/92 (95.7)	N/F	92/92 (100)	92/92 (100)	65/92 (71)	N/F
14	Molina *et al.* (2007)	N/F	N/F	N/F	N/F	6/15 (40)	N/F	N/F	N/F	6/15 (40)	N/F
15	Ritmeijer *et al.* (2011)	N/F	N/F	N/F	N/F	N/F	N/F	N/F	N/F	N/F	N/F
	Total	265/504 (53)	479/660 (73)	127/496 (26)	211/537 (39)	513/588 (87)	321/603 (53)	698/911 (77)	364/477 (76)	589/923 (64)	68/362 (19)

n (%), number and percentage; N/F, not found; –/–, number of events and total value; 'ID' number (identifier for each included paper).

Table 6. Most used tests in the diagnosis of VL in coinfected patients

		Diagnostic methods						
		Parasitological			Serological			
			Marrow puncture, *n* (%)					
ID number	Author (year)	Spleen examination, *n* (%)	Direct examination	Culture	PCR, *n* (%)	IFAT, *n* (%)	rk39, *n* (%)	N/F, *n* (%)
1	Távora *et al.* (2015)	N/F	34/42 (80,5)	N/F	N/F	N/F	28/42 (67)	N/F
3	Cota *et al.* (2014)	N/F	N/F	N/F	N/F	N/F	N/F	25/46 (54)
4	Lima *et al.* (2013)	N/F	124/224 (55)	152/187 (81)	N/F	113/150 (75)	N/F	N/F
6	Alexandrino-de-Oliveira *et al.* (2010)	N/F	20/23 (87)	23/23 (100)	N/F	N/F	N/F	N/F
7	Burza *et al.* (2014*a*, 2014*b*)	N/F	128/159 (81)	N/F	N/F	N/F	31/158 (19)	N/F
8	Diro *et al.* (2014*a*, 2014*b*)	42/57 (78)	10/57 (19)	N/F	N/F	N/F	N/F	N/F
9	Mahajan *et al.* (2015)	63/102 (62) marrow, spleen or liver		N/F	N/F	N/F	39/102 (38)	N/F
10	Bourgeois *et al.* (2008)	N/F	N/F	21/27 (78)	27/27 (100)	N/F	N/F	N/F
11	Sinha *et al.* (2011)	N/F	43/55 (78)	N/F	N/F	N/F	43/55 (78)	N/F
13	Hurissa *et al.* (2010)	44/48 (92)	25/48 (52)	N/F	N/F	N/F	23/48 (49)	44/48 (92)
	Molina *et al.* (2007)	N/F	15/15 (100)	N/F	N/F	N/F	N/F	N/F
	Total	86/105	9/15 = 399/623 (64)	196/237	27/27 (100)	113/150 (75)	164/405 (40)	69/94 (73)
		Parasitological 771/1094 (70)				Serological 346/649 (53)		
	Total of tests performed	771/1117 (69)				346/1117 (31)		

IFAT, indirect immunofluorescence test; PCR, polymerase chain reaction; rK39, recombinant antigen rapid test; N/F, not found; *n* (%): number and percentage; 'ID' number (identifier for each included paper).

analysed literature were found three articles that mentioned this technique: two of them were carried out in Ethiopia, in which the authors (ID: 8, 9) diagnosed amastigotes in spleen aspirates in 78% and 92% of patients, respectively. In India (ID: 9), the coinfection was confirmed in 63% of the patients. The number of patients diagnosed by biopsy of spleen, liver or bone marrow aspiration were not specified. The absence of data regarding aspiration of spleen or liver can be related to the lack of trained personnel to perform this technique in safely way, as well as, interpretation of the results.

In nine studies, the diagnosis carried out through parasites detection in bone marrow aspirates/or isolation of parasite in this tissue, which were superior to the serological method. In some studies, the patients were submitted to two diagnostic methods. When diagnosing, its necessary to consider the monitoring time throughout the treatment, considering the severity of infection into account, such as the use of HAART, different types of populations, where the disease may have been diagnosed at a later stage by HIV as well as different antibody concentrations, which may be related to different age, nutritional and/or immune status patterns of the subject.

The data from this review allowed observing the authors' experience with both parasitological and serological diagnostic tests for detecting the presence of LV infection in HIV patients. However, the serological tests were less used than the parasitological examinations. These data reflect the low sensitivity of the already recognized serological tests for the diagnosis of VL among coinfected patients with LVH/HIV.

Among the blood tests mentioned in the studies (Table 7), the most frequent findings were low haemoglobin/anaemia (88%) (ID: 1, 3, 4, 5, 6, 7, 8, 9, 11, 15), thrombocytopenia (81%) (ID: 1, 3, 5, 6, 12, 13), leukopenia (89%) (ID: 1, 3, 4, 5, 6, 12, 13), increased creatinine (57%) (ID: 1, 3, 4, 5, 9, 11), viral load detected (61%) (ID: 1, 3, 6, 10, 14), Increased bilirubin (97%) (ID: 3, 4, 6, 9), glutamic oxalacetic transaminase (GOT) (76%) (ID: 3, 4, 5, 9) and pyruvic glutamic transaminase (PGT) (76%) (ID: 4, 5, 9, 11).

The moment of diagnosis of HVL in HIV patients (Table 8) was mentioned in only six articles (ID: 1, 4, 6, 7, 9, 10). In these studies, in a total of 577 patients, 267 (46%) were diagnosed after HIV diagnosis and 311 (54%) were diagnosed concomitantly.

Quantification of $CD4^+$ lymphocytes was reported in 13 studies (ID: 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15), in which 86% (592/511) had <200 cells mm^{-3}. Of these, 51% (193/394) were <100 cells mm^{-3}. The mean $CD4^+$ lymphocyte count was 165, mentioned in four studies (ID: 1, 7, 10, 15) and the median and interquartile range were 89 (52.7–176), cited by ten studies (ID: 3, 5, 6, 7, 8, 9, 10, 11, 12, 14). No study showed significant differences between $CD4^+$ T cell count and relapse rate.

HAART (Table 8), mentioned in 12 studies (ID: 1, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15), was used in 91% (650/717) of the patients, of whom only 40% were in use at the time of LV diagnosis and 51% (373/728) started using HAART soon after diagnosis or after treatment. 20% (54/271), mentioned in five studies (ID: 7, 9, 10, 11, 15), had never used it for various reasons and 8% did not report the antiretroviral therapy (13/159) (ID: 7).

Discussion

The first case of coinfection was described in Europe in 1985 and later in 35 countries, with a continuous increase of cases after 1990 due to the geographical overlap of LVH and HIV (Coutinho *et al.*, 2017). In 2015, the WHO reported that visceral leishmaniasis (VL) is present in 56 countries, and in 90% of cases it occurs in seven countries such as Brazil, Ethiopia, Kenya, India, Sudan, Somalia and South Sudan (World Health Organization, 2015; Machado *et al.*, 2016). Global HIV incidence reached its

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Table 7. Main haematological findings presented by patients with LV/HIV coinfection

ID number	Author (year)	Haemoglobin *n* (%)	Leukopenia *n* (%)	Thrombocytopenia *n* (%)	Creatinine *n* (%)	Viral load *n* (%)	Bilirubin *n* (%)	GOT *n* (%)	PGT *n* (%)
1	Távora *et al.* (2015)	40/42 (95) 7.9[a]	30/42 (71) 1756[a]	26/42 (63) 62 792[a]	9/41 (22) 1.1[a]	23/42(55) 82 915[a]	N/F	N/F	N/F
3	Cota *et al.* (2014)	*n* 46/8.2[b] (7.2–9) [c]	*n* 46/2000[b] (1575–2800)[c]	*n* 46/114 500[b] (82 750– 173 000)[c]	*n* 46	30/46 (65)	*n* 46	*n* 46	N/F
					0.8[b] (0.7–1.1)[c]	3.8[a] ± 1.2 $\log^{10}$	0.6[b] (0.5–1.1)[c]	44[b] (27.2–61.7)[c]	
4	Lima *et al.* (2013)	243/250 (97)	224/251 (89)	139/204 (68)	56/211 (26.5)	N/F	243/250 (97)	131/224 (59)	131/224 (59)
5	de Souza *et al.* (2012*a*, 2012*b*)	17/27 (63)	23/27 (85)	17/27 (63)	*n* 27	N/F		*n* 27	*n* 27
		8.4[a] (1.9)[d]	2341[a] (1101)[d]	142, 148[a]	1.0[a]			77.5[a]	47.9[a]
				(65.706)[d]	(0.5)[d]			(60.4)[d]	(25.8)[d]
6	Alexandrino-de-Oliveira *et al.* (2010)	16/20 (80)	14/20 (70)	11/20 (55)	N/F	18/20 (88)	16/20 (80)	N/F	N/F
7	Burza *et al.* (2014*a*, 2014*b*)	<6 = 22/159 (14), 6–8 = 58/159 (37)	N/F	N/F	N/F	N/F	N/F	N/F	N/F
8	Diro *et al.* (2014*a*, 2014*b*)	35/55 (64), 9.4[b] (7.9–10.6)[c]	N/F	N/F	N/F	N/F	N/F	N/F	N/F
9	Mahajan *et al.* (2015)	<6 = 16/102 (16)	N/F	<150 000 = 46/89 (52)	<1.2 = 81/97 (84)	N/F	⩾1.9 = 1/68 (2)	<46 = 38/92 (41.3)	<48 = 77/92 (41)
		6–7 = 32/102 (31)		⩾150 000 = 39/89 (48) 146 000[b] (109 500–202 500)[c]	1.2–2 = 11/97 (11.3)>2 = 5/97 (5)		0.5–1.9 = 28/68 (41)	>46–200 = 52/92 (56.5)	>48–200 = 14/92 (56.5)
		⩾8 = 54/102 (53)					<0.5 = 39/68 (57)	>200 = 2/92 (2.2)	>200 = 1/92(2.2)
		8.2[b] (6.4–9.7)[c]						51[b] (35.3–66.7)[c]	26.3[b] (17.1–39.3)[c]
10	Bourgeois *et al.* (2008)	N/F	N/F	N/F	N/F	16/27 (41) 161.250[b] (<400– 950 000)[e]	N/F	N/F	N/F
11	Sinha *et al.* (2011)	*n* 55, 7.9[b] (6.9–9.3)[c]	N/F	*n* 50/124 000[b] (100 000– 166 000)[c]	*n* 49, 0.9[b] (0.7–1.1)[c]	N/F	N/F	N/F	*n* = 49, 25[b] (19–38)[c]
12	Diro *et al.* (2015)	*n* 74/8.9[b] (7.1–10.8)[c]	*n* 74 / 2600[a] (2300–3620)[c]	*n* 74, 192[b] (136–274)[c]	N/F	N/F	N/F	N/F	N/F
13	Hurissa *et al.* (2010)	N/F	45/51 (88)	30/39 (77)	N/F	N/F	N/F	N/F	N/F
14	Molina *et al.* (2007)	N/F	N/F	N/F	N/F	<50 = 8/21 (38)	N/F	N/F	N/F
15	Ritmeijer *et al.* (2011)	*n* 195/7.6[b] (2.5–3.1)[c]	N/F	N/F	N/F	N/F	N/F	N/F	N/F
	Total	11/15 = 903/1025 (88)	7/15 = 456/511 (89)	9/15 = 478/591 (81)	6/15 = 268/ 471 (57)	5/15 = 95/156 (61)	4/15 = 373/384 (97)	4/15 = 294/389 (76)	4/15 = 298/392 (76)
		6/15 = 8.3[b] (6.3–10.4)[c]	2/15 = 2048[a]	2/15 = 102 470[a]	2/13 = 1.05[a]			2/15 = 47.5[b] (31.2–64.2)[c]	2/15 = 25.6[b] (18–38.6)
		2/15 = 8.1[a]	2/15 = 2300[b] (1937–3210)[c]	4/15 = 144 125[b] (107 062–203 875)	2/15 = 0.8[b] (0.7–1.1)[c]				

GOT, glutamic oxalacetic transaminase; PGT, pyruvic glutamic transaminase; *n* (%): number and percentage; N/F: not found; 'ID' number (identifier for each included paper).
[a]Average.
[b]Median.
[c]Interquartile range.
[d]Standard deviation.
eExtreme.

peak in 1997, at 3·3 million new infections. Annual incidence has stayed relatively constant at about 2·6 million per year since 2005, after a period of fast decline between 1997 and 2005. The number of people living with HIV/AIDS has been steadily increasing and reached 38·8 million in 2015. At the same time, HIV/AIDS mortality has been declining at a steady pace, from a peak of 1·8 million deaths in 2005 to 1·2 million deaths in 2015 (Wang *et al.*, 2016). With the presence of HIV, the risk of coinfection increases from 100 to 2320 times. In endemic countries, the rate is between 2 and 9%, but in neglected populations, this rate may be even higher if it is not on the list of opportunistic diseases associated with HIV (Viana *et al.*, 2017).

Geographical overlap of HVL and the HIV, the consequent emergence of coinfection of these diseases, has become a public health problem with high morbidity and mortality rates (Alvar *et al.*, 2008; Martins-Melo *et al.*, 2014). Since 1987, dozens of cases of HVL/HIV have been described in Brazil and other parts of the world (Ministério da Saúde, 2014; World Health Organization., 2015). Coinfection has modified the epidemiological profile due to the expansion of leishmaniasis from rural to urban areas, places with higher HIV prevalence and expanded among developing countries (Carvalho *et al.*, 2014; Ministério da Saúde., 2015; Druzian *et al.*, 2015), as well as developed countries (Herrador *et al.*, 2015). According to the search criteria used, only two studies in Europe were found included among the inclusion criteria, different from the cases described in the scientific literature with the prevalence and effective distribution of LV/HIV coinfection, much more frequent in African countries than in Europe (de Albuquerque *et al.*, 2014; Martins-Melo *et al.*, 2014).

Of the studies performed, most (6%) occurred in Brazil (Lima *et al.*, 2013; de Albuquerque *et al.*, 2014), four (27%) in Ethiopia (Hurissa *et al.*, 2010; Ritmeijer *et al.*, 2011; Diro *et al.*, 2014*a*, 2015), three (20%) in India (Sinha *et al.*, 2011; Burza *et al.*, 2014*a*; Mahajan *et al.*, 2015) and only two studies in developed countries, one (7%) in Spain (Molina *et al.*, 2007) and one in France (Bourgeois *et al.*, 2008). A total of 13 studies were carried out in developing countries, differing from data released by the WHO, which reports higher coinfection rates in developed countries such as Spain, France, Italy and Portugal (de Albuquerque *et al.*, 2014; Martins-Melo *et al.*, 2014). The states that have notified higher rates of HVL have also reported HIV coinfection (Alexandrino-de-Oliveira *et al.*, 2010; Ministério da Saúde., 2015).

Most of the coinfected patients were males, 86%, a rate lower than the rate reported by the Ministry of Health (BMH), 91.6% (Diro *et al.*, 2014*b*; Ministério da Saúde., 2015). The number of HIV cases among women increased, explaining this change in the gender proportional difference of patients with HVL/HIV (Carvalho *et al.*, 2013). The greater male susceptibility may be related to socioeconomic, behavioural and environmental factors, with respect to habit and exposure to the vector due to the type of work among others, but it is still a matter of debate (Martins-Melo *et al.*, 2014). Men generally have greater vulnerability to some diseases compared with women. However, in 19 years, this difference is not very clear; the susceptibility to becoming ill seems to be similar in all sexes. However, this vulnerability is most notable after 20 years, when adult males are most affected. Males were more vulnerable to Leishmania/HIV coinfection, with 78% of cases reported in the period 2002–2006. This proportion is similar to Europe which showed that 83% of coinfection cases occurred in males. A study done in Brazil showed that males contributed 78% of the cases of coinfection between 2001 and 2005. The higher incidence in males can be explained in part by the masculinization of AIDS and visceral leishmaniasis, the most vulnerable. There were four deaths from coinfection, three of them were male (Botelho and Natal, 2009). In a review article, Lindoso *et al.*, described that the prevalence of LVH/HIV coinfection in young men is reported in all cohorts and that in Brazil the highest incidence is found among young men between the 29 and 49 years old (Lindoso *et al.*, 2016), gender and age group most affected by HIV.

The mean age and median were around 34 years, lower than that reported by the BMH, mean age of 38 years (Ministério da Saúde., 2015). HVL/HIV mainly affects adults between the ages of 30 and 50 (Martins-Melo *et al.*, 2014). The probability of death is higher in patients over 45 years, possibly because the immune system is less efficient in the control of infections (de Albuquerque *et al.*, 2014).

HVL may contribute to the rapid development of AIDS, leading to increased viral load in the bloodstream (de Almeida e Cavalcanti *et al.*, 2012; Santos-Oliveira *et al.*, 2013). HIV infection increases the risk of developing HVL from 100 to 2320 times in endemic regions (Ministério da Saúde, 2015). *Leishmania*/HIV coinfection in the same macrophage makes it difficult to control *Leishmania* infection (Santos-Oliveira *et al.*, 2010; Druzian *et al.*, 2015), favouring the progression of one or both diseases (World Health Organization., 2010, 2015; Van Griensven *et al.*, 2014*c*), possibly due to a chronic activation of the immune system (Craft *et al.*, 2010; Martins-Melo *et al.*, 2014), which results in T cell depletion (Santos-Oliveira *et al.*, 2010). HVL/HIV coinfection reduces therapeutic response and increases the number of relapses, especially when the number of $CD4^+$ T lymphocytes is <200 cells mm^{-3} (Craft *et al.*, 2010; de Souza *et al.*, 2012*a*; Ministério da Saúde., 2015).

Clinical manifestations found in this study, such as fever, splenomegaly, weight loss, asthenia, anaemia and/or pallor, hepatomegaly, cough and diarrhoea were similar to the information mentioned by other studies (Granthon *et al.*, 2007; Craft *et al.*, 2010; Dupnik *et al.*, 2011; de Souza *et al.*, 2012*a*), except for splenomegaly (91%), which in this review was lower. Clinical manifestations are generally similar between HVL and HVL/HIV, except for the presence of more frequent diarrhoea in coinfection (de Souza *et al.*, 2012*a*; Lima *et al.*, 2013; de Albuquerque *et al.*, 2014), which may be associated with intestinal infections, concomitant use of antibiotics and/or antiretrovirals (de Souza *et al.*, 2012*a*), as well as with parasitism of *Leishmania* amastigotes in intestinal mucosal cells, increasing permeability (Santos-Oliveira *et al.*, 2011, 2013).

Other opportunistic diseases such as malaria (Costa *et al.*, 2013*a*), tuberculosis, pneumocystosis, cryptococcosis, Chagas disease and toxoplasmosis may present a clinical picture similar to that of HVL, making clinical diagnosis of coinfection difficult (Costa *et al.*, 2013*b*; Cota *et al.*, 2014; Martins-Melo *et al.*, 2014). Some clinical manifestations such as prolonged fever, visceromegaly and pancytopenia, common in patients with HIV-negative HVL, are not always present in patients coinfected with HVL/HIV (de Souza *et al.*, 2012*a*; de Albuquerque *et al.*, 2014), associated with deficiency of proliferative mononuclear cells in these organs (Alexandrino-de-Oliveira *et al.*, 2010; Cota *et al.*, 2014).

The most frequent diagnostic tests were parasitological tests (67%), of which the marrow aspirate was referred to in ten studies, only three in culture. Serological tests were less used (33%); only six studies used the rK39 test. The rK39 test was a major advance in the diagnosis of HVL; however, there are still insufficient data to prove its efficacy in the diagnosis in HVL/HIV coinfected patients (Cota *et al.*, 2012). The practical and effective rK39 can be used in decentralized environments, in community or fieldwork (Cota *et al.*, 2012), but it is not recommended by the BMH because it reaches only 45% of sensitivity in coinfected patients from Brazil, 77% in Ethiopia and 100% in India (Ministério da Saúde., 2015). The diagnosis of coinfection is difficult due to the intense parasitism in circulating macrophages, with little antibody response. Thus, direct examination of material

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Table 8. Moment of HVL diagnosis and HAART-related $CD4^+$ cell count

ID number	Author (year)	Moment of LV diagnosis		Count of $CD4^+$ cell cells per mm^3, *n* (%)		HAART regarding the VL diagnosis
		After HIV diagnosis no. (%)	Concomitant no. (%)			
1	Távora *et al.* (2015)	24/42 (57)	16/42 (38)	<100 = 15/42 (36)	183[a]	31/42 (73.8)
			1st VL = 2/42 (5)	100–200 = 11/42 (26)		Before 20/31 (65)
			P = 0.05	>200 = 16/42 (38)		After 11/31 (35)
						Months 7.6[b]
3	Cota *et al.* (2014)	N/F	N/F	N/F	91[b] (39–194)[c]	Before 30/46 (65)
4	Lima *et al.* (2013)	100/224 (44.6)	124/224(55.4)	<50 = 13/47 (27.6)	N/F	N/F
				50–199 = 25/47 (53.2)		
				200–499 = 7/47 (14.9)		
				>499 = 2/47 (4.3)		
5	de Souza *et al.* (2012*a*, 2012*b*)	N/F	N/F	22 (81.5)	123[b] (66–280)[c]	N/F
6	Alexandrino-de-Oliveira *et al.* (2010)	13/23 (57)	10/23 (43)	<200 = 16/20 (80)	44.5[b] (5–460)[d]	Before 8/23 (34.8)
				>200 = 4/20 (20)		After 15/23 (65.2)
7	Burza *et al.* (2014*a*, 2014*b*)	60/159 (38)	99/159 (62)	122/159 (76.7)	122[a]	Before 39/159 (25)
				<100 = 56/122 (46)	111[b] (59–193)[c]	After 84/159 (53)
				100–199 = 36/122 (29.5)		Never 23/159 (14)
				200–349 = 23/122 (18.9)		Unknown 13/159 (8)
				⩾350 = 7/122 (5.7)		
8	Diro *et al.* (2014*a*, 2014*b*)	N/F	N/F	Before <200 = 53/57	61[b] (35–101)[c]	Before 36/57 (63.2)
				<100 = 39/53 (74)		After 21/57 (36.8)
				100–200 = 14/53 (26)		
9	Mahajan *et al.* (2015)	58/102 (56.9)	47/102 (43.1)	<100 = 22/73 (30.1)	169[b] (88–230)[c]	Before 52/102 (51)
				100–200 = 27/73 (37)		After 42/102 (41)
				200–350 = 16/73 (21.9)		Never 8/102 (8)
				⩾350 = 8/73 (11)		
10	Bourgeois *et al.* (2008)	12/27 (44)	15/27 (56)	<200 = 26/27 (96)	200[a]/51[b] (4–322)[d]	Before 12/27 (44)
				>200 = 1/27 (4)		After 14/27 (52)
						Never 1/27 (4)
11	Sinha *et al.* (2011)	N/F	N/F	<200 = 48/53 (90.6)	66[b] (38–112)[c]	Before 3/55 (5)
				>200 = 5/53 (9.4)		After 47/55 (86)
						Never 5/55 (9)
12	Diro *et al.* (2015)	N/F	N/F	<100 = 40/61 (66)	70[b] (44–125)[c]	After 72/74 (97)
				100–200 = 21/61 (34)		
13	Hurissa *et al.* (2010)	N/F	N/F	34/92 (37)	N/F	Before 22/92 (23.9)
				<50 = 11/34 (32)		After 31/92 (55.7)
				50–200 = 23/34 (68)		
				>200 = 58/92 (63)		
14	Molina *et al.* (2007)	N/F	N/F	<200 = 20/21 (95)	104[b] (4–300)[d]	Before 13/21 (62)
				>200 = 1/21 (5)		After 8/21 (38)
15	Ritmeijer *et al.* (2011)	N/F	N/F	<100 = 21/43 (49)	155[a]	Before 42/87 (48)
				100–200 = 22/43 (51)	123[e]	After 28/87 (32)
						Never 17/87 (20)
	Total	6/15 = 267/577 (46)	6/15 = 311/577 (54)	6/15 = < 100–193/394 (51)	4/15 = 660[a]	12/15 = 635/758 (82)
			1st VL = 2/577 (1)	12/15 = <200–511/592 (86)	10/15 = 89[b]	

(*Continued*)

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Table 8. (*Continued.*)

ID number	Author (year)	Moment of LV diagnosis: After HIV diagnosis no. (%)	Moment of LV diagnosis: Concomitant no. (%)	Count of CD4$^+$ cell cells per mm^3, *n* (%)		HAART regarding the VL diagnosis
				9/15 = >200–132/460 (29)	7/15[c] = (52.7–176)	11/15 = before – 277/700 (40)
					3/15[d] = (4–360)	11/15 = after – 373/728 (51)
						4/15 = never – 54/271 (20)
						1/15 = unknown 13/159 (8)
						In use = 650/717 – (91)
						No use = 67/717 – (9)

n (%), number and percentage; N/F, not found; HAART, highly active antiretroviral therapy; 'ID' number (identifier for each included paper).
[a]Average.
[b]Median.
[c]IQR: interquartile range.
[d]Extreme.
[e]Standard deviation.

obtained through bone marrow, spleen, liver or lymph nodes aspirate is the most effective, under direct visualization on slides of *Leishmania* parasites in the amastigote form (World Health Organization., 2010; Lindoso *et al.*, 2014; Druzian *et al.*, 2015); identification of the parasite around 94% (Lima *et al.*, 2013; Ministério da Saúde., 2015; Fontoura *et al.*, 2016). *Leishmania* parasites identification in the spleen, bone marrow or liver is incontestable proof to confirm the coinfection (Cota *et al.*, 2012). However, in a study, Alexandrino-de-Oliveira *et al.* (2010), only managed to isolate the parasite in three patients. Nevertheless, performing the puncture of bone marrow or other organs requires trained personnel. Besides, it is an invasive and painful technique (Cota *et al.*, 2013*b*). Parasitological diagnosis in culture is more sensitive to detect the parasite; however, it can delay the start of treatment and consequently impair the patient's probability of survival (Lima *et al.*, 2013).

Serological tests are more reliable for diagnosis in HVL (Cota *et al.*, 2013*a*); however, they are less safe in cases of HLV/HIV coinfection (World Health Organization., 2010; Cota *et al.*, 2012) because they offer sensitivity around 55% (Lindoso *et al.*, 2014), since they use crude and recombinant *Leishmania* antigens (de Souza *et al.*, 2012*a*; Cota *et al.*, 2013*b*). A positive reaction may be only a serological scar (Ministério da Saúde., 2015). Ideally, all VL patients should undergo HIV testing and vice versa (Lima *et al.*, 2013; Coura-Vital *et al.*, 2014). A haemogram with pancytopenia in HIV patients suggests HLV coinfection, although zidovudine and some disseminated infections may also lead to this change (Lima *et al.*, 2013). Puncture of spleen and liver were reported only in three studies (Hurissa *et al.*, 2010; Diro *et al.*, 2014*a*; Mahajan *et al.*, 2015). Cytological examination of the liver and spleen is faster, shows excellent results, but offers greater risks of haemorrhage and death (Cota *et al.*, 2014; Barbosa Júnior *et al.*, 2015), especially in patients with advanced stage of disease (Lima *et al.*, 2013).

Of the articles studied, 12 reported a decrease in CD4$^+$ T cell count below 200 cells dL^{-1} in 86% of the cases, of which 51% were < 100 cells dL^{-1}; the mean of the total was around 155 cells dL^{-1}. Compared with people infected with only HVL and undergoing treatment with leishmanicides, coinfected patients had lower antibody titres (World Health Organization., 2010; Nascimento *et al.*, 2011). Individuals with cell counts above 100 cells mL^{-1} are associated with decreased relapse rate (Cota *et al.*, 2011). HAART helps increasing CD4$^+$ T cells, but in VL/HIV patients, cells may continue to be low even during clinical remission (Santos-Oliveira *et al.*, 2010).

Treatment may have low therapeutic responses and frequent relapses (de Souza *et al.*, 2012*a*; Das *et al.*, 2014; World Health Organization., 2015) due to bone marrow depletion (Botelho and Natal, 2009), causing simultaneous occurrence of the two microorganisms that affect the entry of new lymphocytes in the peripheral blood, which explains the presence of CD4$^+$ lower than 200 cells dL^{-1}, already at the beginning of the treatment (Santos-Oliveira *et al.*, 2010). All studies occurred after the HAART introduction period in 1996 (Cota *et al.*, 2011). Early use of HAART is a strategy recommended by WHO (Van Griensven *et al.*, 2014*b*; World Health Organization, 2015). However, relapses may occur even after therapy and prophylaxis, and when HAART is used (Coura-Vital *et al.*, 2014; Barbosa Júnior *et al.*, 2015), however, 48% of HIV-infected patients have contracted VL, even when in use of HAART. Nevertheless, it does not seem to completely prevent relapse (Dupnik *et al.*, 2011), since 20% had relapses, and 91% of coinfected patients were using HAART during follow-up, suggesting that the presence of the parasite may affect both diseases (Santos-Oliveira *et al.*, 2010). The BMH and the WHO suggest that HAART should be done after HVL treatment and patient stabilization both clinically and haematologically (Ministério da Saúde., 2015).

Treatment was reported in 1171 patients with HVL/HIV, 18% of whom were treated with amphotericin B deoxycholate, 642 (47%) with liposomal amphotericin B and 233 (17%) with Sb^v (Glucantime®), sodium stibogluconate 95 (7%), miltefosine 143 (10%) and paromomycin 9 (1%). The first three were the drugs used in Brazil. Only 34 (8%) of the treatments used amphotericin B liposomal therapy, which has been indicated by the BMH only since 2013 (there is still no scientific evidence to establish the optimal dose) (Ministério da Saúde., 2015), based on the benefits of liposomal formulation compared with other drugs (Coura-Vital *et al.*, 2014; Druzian *et al.*, 2015; Távora *et al.*, 2015). The most widely used drug was amphotericin B deoxycholate, in 222 (51%) cases, previously recommended, in 2011 (de Albuquerque *et al.*, 2014; Martins-Melo *et al.*, 2014), and Sb^v/Glucantime® in 179 (41%) cases.

In a review study, Cota *et al.* (de Almeida Pachioni *et al.*, 2013) reported that, according to available data, there was a higher mortality rate among patients treated with Sb^v than in those treated with amphotericin B. In the countries of Ethiopia, India and Spain, liposomal amphotericin B was the drug used to treat 605 (65%) coinfected patients, with the lowest number, 149 (16%), of the use of Sb^v or miltefosine, 143 (15%). In a systematic review study done in Ethiopia, the combined treatment between

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liposomal amphotericin B and miltefosine was shown to be promising, followed by secondary prophylaxis (Diro *et al.*, 2014*b*). Miltefosine is the only oral leishmanicide available for the treatment of HVL and HVL/HIV (Castelo Branco *et al.*, 2016).

Liposomal amphotericin B is indicated for patients over 50 years of age, with renal insufficiency, heart disease, signs of severity, in which the Sb^{v}, is contraindicated (de Albuquerque *et al.*, 2014; Druzian *et al.*, 2015; Ministério da Saúde., 2015). Liposomal amphotericin B is formulated into a liposome and cholesterol in a liposome controls bilayer permeability, which comprises drug enveloping in a layer of cholesterol and other phospholipids, favouring stability in blood, macrophages and tissues, for greater penetration efficiency of a drug in the tissues, especially in liver and spleen, where the use of lipoma favours the targeting of drugs to phagocytic cells, which are *Leishmania* host cells (Cota *et al.*, 2013*a*). Complications of Sb^{v} therapy are increased in HVL/HIV patients (Alexandrino-de-Oliveira *et al.*, 2010; Inocêncio *et al.*, 2011; de Souza *et al.*, 2012*a*), and maybe a cause-and-death factor (Martins-Melo *et al.*, 2014). New treatment options have been researched to minimize side-effects and complications in patients with HVL/HIV coinfection (Almeida-Souza *et al.*, 2016).

Of the 15 studies, 14 reported recurrence in 229 of 1140 (20%) patients. According to Druzian *et al.*, recurrences occur when patients are treated with the recommended therapy and within 12 months they present again the symptoms of the disease (Druzian *et al.*, 2015). A study reported relapse rates in 9.1% of HVL/HIV to 1.5% in non-HIV VL (Martins-Melo *et al.*, 2014). In another study, 37% in VL/HIV and 2.5% in LV (Cota *et al.*, 2014). Even after treatment, some parasites may remain within the macrophage (Druzian *et al.*, 2015), in the bone marrow (Santos-Oliveira *et al.*, 2013), one patient presented positive PCR result even 5 years after treatment (Silva *et al.*, 2013). Patients with HVL/HIV generally take longer to achieve deoxyribonucleic acid (DNA) negativity following specific therapy than patients with non-HIV HVL, which favours frequent relapses in coinfected patients (Santos-Oliveira *et al.*, 2013).

Liposomal amphotericin B is the drug indicated in the secondary prophylaxis, every 2 weeks, for patients with cell counts <350 $CD4^{+}$ T lymphocytes per mm^{3}. It prevents recurrences without prophylaxis from 67 to 31% (Cota *et al.*, 2011, 2014; Druzian *et al.*, 2015; Ministério da Saúde, 2015); however, only four studies have reported on the use of secondary prophylaxis and only two (Bourgeois *et al.*, 2008; Cota *et al.*, 2014) have used liposomal amphotericin B. The prophylactic drug should remain in use for at least 6 months or until the $CD4^{+}$ T cell count is above 350 cells dL^{-1} (Cota *et al.*, 2014). Even after an effective treatment, $CD4^{+}$ cell count may remain low (Druzian *et al.*, 2015). The reappearance of classic symptoms, usually after treatment, suggests relapse, with confirmation by parasitological examination of bone marrow aspirate (Ministério da Saúde., 2015). There is no recommendation to repeat the parasitological examination at the end of treatment for confirmation of cure (Druzian *et al.*, 2015).

Cure criteria are not uniform across studies (Ministério da Saúde., 2015). They are usually based on the remission of signs and symptoms such as fever, hepatosplenomegaly, improvement of the general condition of the patient and blood cell counts (Cota *et al.*, 2014; Druzian *et al.*, 2015). In this review study, the authors based on the same criteria for deciding cure, such as remission of signs and symptoms of VL in relation to the presence of fever, hepatosplenomegaly, complete resolution of clinical and haematological parameters, and absence of recurrence after 6 months to 1 year of follow-up. All studies showed the number of patients cured, 781 out of 1147 (68%). HVL/HIV is characterized by low cure rates, around 78% (Sinha *et al.*, 2011; de Albuquerque *et al.*, 2014; Távora *et al.*, 2015). According to the BMH, they are essentially clinical and not all symptoms regress at the end of treatment. The disappearance of fever and improvement of the general condition after the first week of treatment is expected to occur. At the end of the second week, cytopenia regression usually occurs, splenomegaly, which usually takes months to complete regression (Ministério da Saúde., 2015). Predictive causes of death can be detected by means of the predictive scoring system (Druzian *et al.*, 2015).

High mortality rates are more frequent in coinfection patients (de Souza *et al.*, 2012*a*; Cota *et al.*, 2014; Távora *et al.*, 2015). Delay in diagnosis and treatment increases the risk of death (de Albuquerque *et al.*, 2014). In total, 182 of 1171 (16%) deaths were reported. Among the most common predictors of death in HIV-free HVL patients, there are jaundice, thrombocytopenia, haemorrhage, HIV coinfection, diarrhoea and neutropenia (Belo *et al.*, 2014). Among the causes of death in coinfected terminally ill patients, the most common are disseminated intravascular coagulation (Costa *et al.*, 2013*a*), septicaemia (Lima *et al.*, 2013), respiratory failure, jaundice (Nascimento *et al.*, 2011), pneumonia, bacterial infections, haemorrhage (Cota *et al.*, 2014; Martins-Melo *et al.*, 2014), oedema (Coura-Vital *et al.*, 2014; Druzian *et al.*, 2015), vomiting, even when treated with recommended therapies (Costa *et al.*, 2013*a*), $CD4^{+}$ T cell count below 200 cells dL^{-1} (Távora *et al.*, 2015), pancreatitis and drug toxicity (de Albuquerque *et al.*, 2014), especially in patients treated with Sb^{+5} (Cota *et al.*, 2013*a*).

As a control measure, coinfection should be investigated in all patients with clinical signs suggestive of HVL for early intervention, using secondary prophylaxis to prevent relapses (Alexandrino-de-Oliveira *et al.*, 2010; Martins-Melo *et al.*, 2014). The WHO recommends that all HIV patients with classic symptoms who are or have been in endemic areas for VL should perform direct research, culture, PCR, serology, as well as, in cases of HVL, perform HIV testing and compulsory notification (World Health Organization., 2010; de Albuquerque *et al.*, 2014) in order to help in the worldwide knowledge of morbidities and mortalities. This will help to consolidate data from institutions such as the Pan American Health Organization (PAHO) and the WHO (de Araújo *et al.*, 2012; de Albuquerque *et al.*, 2014; Das *et al.*, 2014). However, control measures are still huge challenges (de Araújo *et al.*, 2012; Fontoura *et al.*, 2016). There is a need for improved surveillance and control of coinfection (Ministério da Saúde., 2015). There have been changes in the epidemiological profile of VL and evidence that both the parasite and the vector have the ability to adapt in different environments (Diro *et al.*, 2014*b*; Castelo Branco *et al.*, 2016). This evidences that there are many obstacles in the control of VL (Menon *et al.*, 2016) and, consequently, HLV/HIV coinfection.

Among the main limitations found in this review, there were few studies with satisfactory data regarding the treatment and a limited number of randomized studies, which impairs the quality of the results. Also, most non-randomized studies presented incomplete data regarding dosage, second therapy, reasons for the change of therapy, prophylaxis, follow-up, clinical manifestations, diagnostic methods, test results, time of diagnosis and HAART. Of the few articles that had odds ratios, the data were not similar, making it impossible to perform a meta-analysis.

Few studies included sequencing of follow-up treatment of patients, showing which drugs were more and/or less effective in terms of cure, relapse and death. The majority had data regarding the use of HAART prior to the diagnosis of HVL, after and/or during treatment, but there was no relationship between these data and the $CD4^{+}$ cell counts before and after, as well as the viral load in order to observe the effectiveness of the treatment and its continuity or not.

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Thus, randomized clinical trials must be performed according to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT), including data from patients with VL and LV/HIV × treatment and follow-up, showing the complete treatment (first and second therapy, prophylaxis) and data on cure, relapses and deaths. In countries where leishmaniasis is endemic, data on clinical manifestations, laboratory test results, types of diagnoses, time of diagnosis of HVL in relation to HIV, use of HAART related to $CD4^+$ T cell count should also be included. The compilation of these data would contribute substantially to the evaluation of the clinical response to the various therapeutic protocols.

Concluding remarks

In conclusion, HVL/HIV coinfection is an emerging and complex public health problem due to high rates of recurrence and mortality, especially in men in the 34-year age group, which has expanded among developing countries. Diagnosis and treatment are still a challenge to public health because of the difficulty in establishing the presence of VL in HIV-infected individuals. Liposomal amphotericin B was the most commonly used drug compared with other drugs. Understanding this coinfection facilitates the orientation of good management of patients, reflecting on the need to intensify surveillance and epidemiological control measures.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003118201800080X

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Conflicts of interest. The authors stated that there are no conflicts of interest

Ethical standards. We report that this study was based on clinical trials described in articles found in databases available on the Web, where all the authors of the studies reported having obeyed the ethical standards.

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