SIMPÓSIO INTERNACIONAL

LEISHMANIOSE VISCERAL:
DESAFIOS PARA O CONTROLE
NO CONTEXTO DA DIVERSIDADE DE CENÁRIOS

Leishmaniose visceral: Diversidade e Controle

Diversidade Clínica e Tratamento

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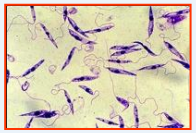
DOENÇA MULTIFATORIAL

Agente Etiológico



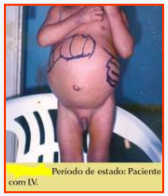
Vetor

Reservatório


Raposa: reservatório silvestre da *Leishmania chagasi*


Cão com emagrecimento, ceratoconjuntivite, lesões de face e orelha.

Hospedeiro susceptível


Período de estado: Paciente com LV.

Alterações Geográficas

Fatores

- **físicos**
- **humanos ou sociais**
- **biológicos**

Risk Factors for Visceral Leishmaniasis among Residents and Migrants in Kafta-Humera, Ethiopia

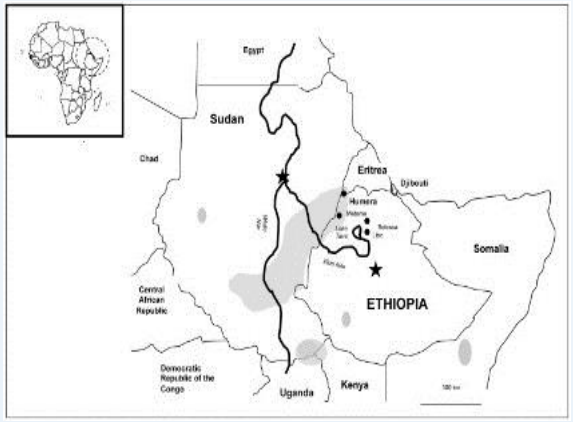


Table 5. Multivariable conditional logistic regression models for factors associated with risk of visceral leishmaniasis among residents and migrants in Humera, Tigray, Ethiopia.

Factor	Matched OR[1]	95% CI[1]	P
Residents			
Always slept under net in rainy season	0.24	0.12–0.48	<.0001
Slept under acacia at night	5.22	1.66–16.42	0.005
Usually slept on ground	2.96	1.20–7.30	0.02
Walls of thatched grass on wood frame	5.30	1.34–21.03	0.02
Monthly expenditure <100 birr per person	3.22	1.42–7.33	0.005
Head of house left school before class 5	2.78	1.17–6.59	0.02
Migrants			
HIV infection[2]	3.98	0.94–16.9	0.06
Ever slept under net	0.20	0.10–0.42	<0.0001
Slept under an acacia at night	4.74	1.88–11.99	0.001
Slept near dogs	6.79	1.83–25.16	0.004
Staple food is porridge (rather than injera)	4.65	2.33–9.29	<0.0001
No formal schooling	5.02	2.59–9.74	<0.0001

[1]Odds ratios (OR) and 95% confidence intervals (CI).
[2]Data on HIV status missing for at least one member of 21 case-control sets; these sets therefore excluded from analysis.
doi:10.1371/journal.pntd.0002543.t005

Citation: Argaw D, Mulugeta A, Herrero M, Nombela N, Teklu T, et al. (2013) Risk Factors for Visceral Leishmaniasis among Residents and Migrants in Kafta-Humera, Ethiopia. PLoS Negl Trop Dis 7(11): e2543. doi:10.1371/journal.pntd.0002543

Prevalence of malnutrition and associated risk factors among adult visceral leishmaniasis patients in Northwest Ethiopia: a cross sectional study

Mengesha *et al. BMC Research Notes* 2014, **7**:75

Table 2 Bivariate and multivariate analysis of possible risk factors with malnutrition among patients with VL in Northwest Ethiopia, 2012

Risk factors	Total	Severely Malnourished		COR (95% CI)	AOR (95%CI)	P-values
		Yes	No			
Eating breakfast						
Always	127 (31.5)*	97 (35.1)	179 (64.9)	1.00	1.00	0.07
Sometimes	276 (68.5)	53 (41.7)	74 (58.3)	1.32 (0.84 – 2.08)	1.56 (0.96 – 2.51)	
Domestic animal						
Present	218 (54.1)	85 (39.0)	133 (61.0)	1.00	1.00	0.48
Absent	185 (45.9)	65 (35.1)	120 (64.9)	0.85 (0.55 – 1.30)	0.99 (0.59 – 1.65)	
Private farm						
Present	168 (41.7)	70 (41.7)	98 (58.3)	1.00	1.00	0.14
Absent	235 (58.3)	80 (34.0)	155 (66.0)	0.72 (0.47 – 1.11)	0.65 (0.38 – 1.11)	
Family size						
≤5	212 (52.6)	79 (37.3)	133 (62.7)	1.00	1.00	0.98#
6-10	185 (45.9)	69 (37.3)	116 (62.7)	1.00 (0.65 – 1.54)	1.12 (0.18 – 6.67)	
≥11	6 (1.5)	2 (33.3)	4 (66.7)	0.84 (0.10 – 5.50)	1.19 (0.21 – 7.05)	
Anemia						
Mild	87 (21.6)	31 (35.6)	56 (64.4)	1.00	1.00	0.42
Moderate	205 (50.9)	72 (35.1)	133 (64.9)	0.98 (0.56 – 1.71)	1.38 (0.76 – 2.52)	
Severe	111 (27.5)	47 (42.3)	64 (57.7)	1.33 (0.71 – 2.47)	1.43 (0.88 – 2.32)	
HIV Status						
Negative	361 (89.6)	130 (36.0)	231 (64.0)	1.00	1.00	0.19
Positive	42 (10.4)	20 (47.6)	22 (52.4)	1.62 (0.81 – 3.21)	1.67 (0.34 – 3.32)	
Intestinal parasites						
Absent	211 (52.4)	50 (23.7)	161 (76.3)	1.00	1.00	0.00
Present	192 (47.6)	100 (52.1)	92 (47.9)	3.50 (2.24 – 5.48)	3.01 (2.20 – 5.11)	

*Figures in parenthesis indicate percentage, # Fisher exact.

Table 3 Intestinal parasites among adult VL patients in Northwest Ethiopia, 2012

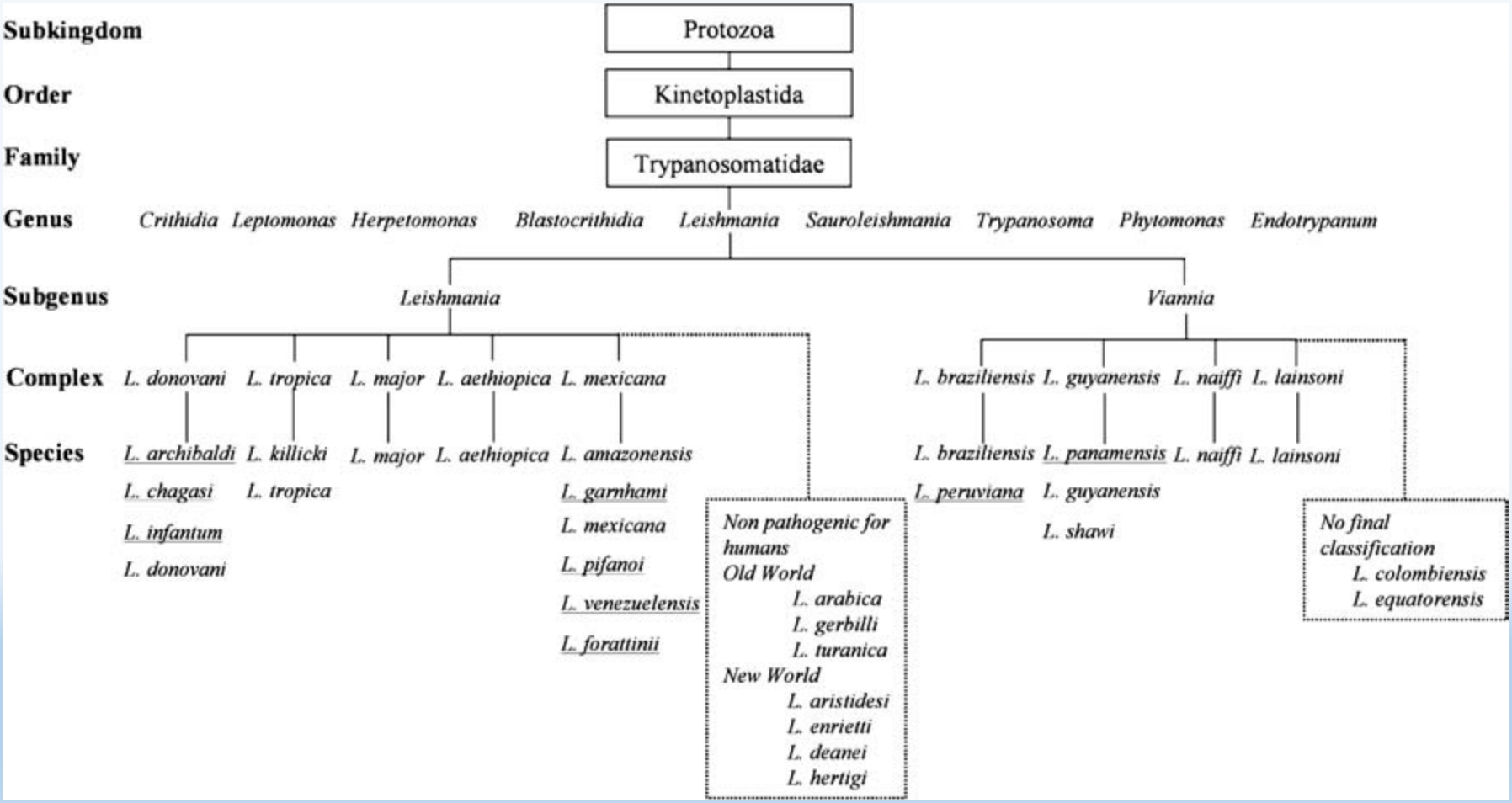
Intestinal parasites	Total Number (%)	Severely malnourished	
		Yes Number (%)	No Number (%)
Protozoas			
Entamoeba histolytica/dispar	40 (9.9)	31 (77.5)	9 (22.5)
Giardia intestinalis	47 (11.7)	34 (72.3)	13 (27.7)
Helminthes			
Ascaris lumbricoides	41 (10.2)	29 (70.7)	12 (29.3)
Hook worm	85 (21.1)	50 (58.8)	35 (41.2)
Hymenolopsis nana	3 (0.7)	2 (66.7)	1 (33.3)
Schistosoma mansoni	4 (1.0)	4 (100)	0 (0.0)
Strongyloide stercolaris	23 (5.7)	14 (60.9)	9 (39.1)
Tanea species	4 (1.0)	4 (100)	0 (0.0)
Trichuris trichiura	4 (1.0)	3 (75.0)	1 (25.0)

Table 4 Multiple parasitic infections among severely malnourished adult VL patients in Northwest Ethiopia, 2012 (N = 48)

Multiple parasitic infections	Frequency
Ascaris lumbricoides + Hook worm	13
Entamoeba histolytica/dispar + *Giardia intestinalis*	7
Entamoeba histolytica/dispar + Hook worm	5
Hook worm + *Strongyloide stercolaris*	4
Giardia intestinalis + Hook worm	4
Giardia intestinalis + *Ascaris lumbricoides*	4
Giardia intestinalis + *Strongyloide stercolaris*	4
Schistosoma mansoni + *Entamoeba histolytica/dispar*	2
Ascaris lumbricoides + *Strongyloide stercolaris*	1
Hymenolopsis nana + *Entamoeba histolytica/dispar*	1
Giardia intestinalis + Hook worm + *Entamoeba histolytica/dispar*	2
Giardia intestinalis + Hook worm + *Strongyloide stercolaris*	1

Conclusions: The prevalence of malnutrition in VL patients was very high and it was associated with intestinal parasitic infections. Therefore, screening of severely malnourished VL patients for intestinal parasitic infections during admission is recommended.

Taxonomia



WHO and Bañuls et al, 2007

Pele

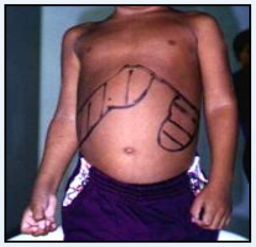
Fagocitose

Neutrófilo

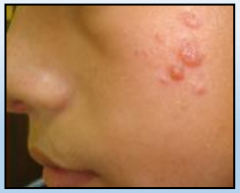
Diferenciação

Macrófago

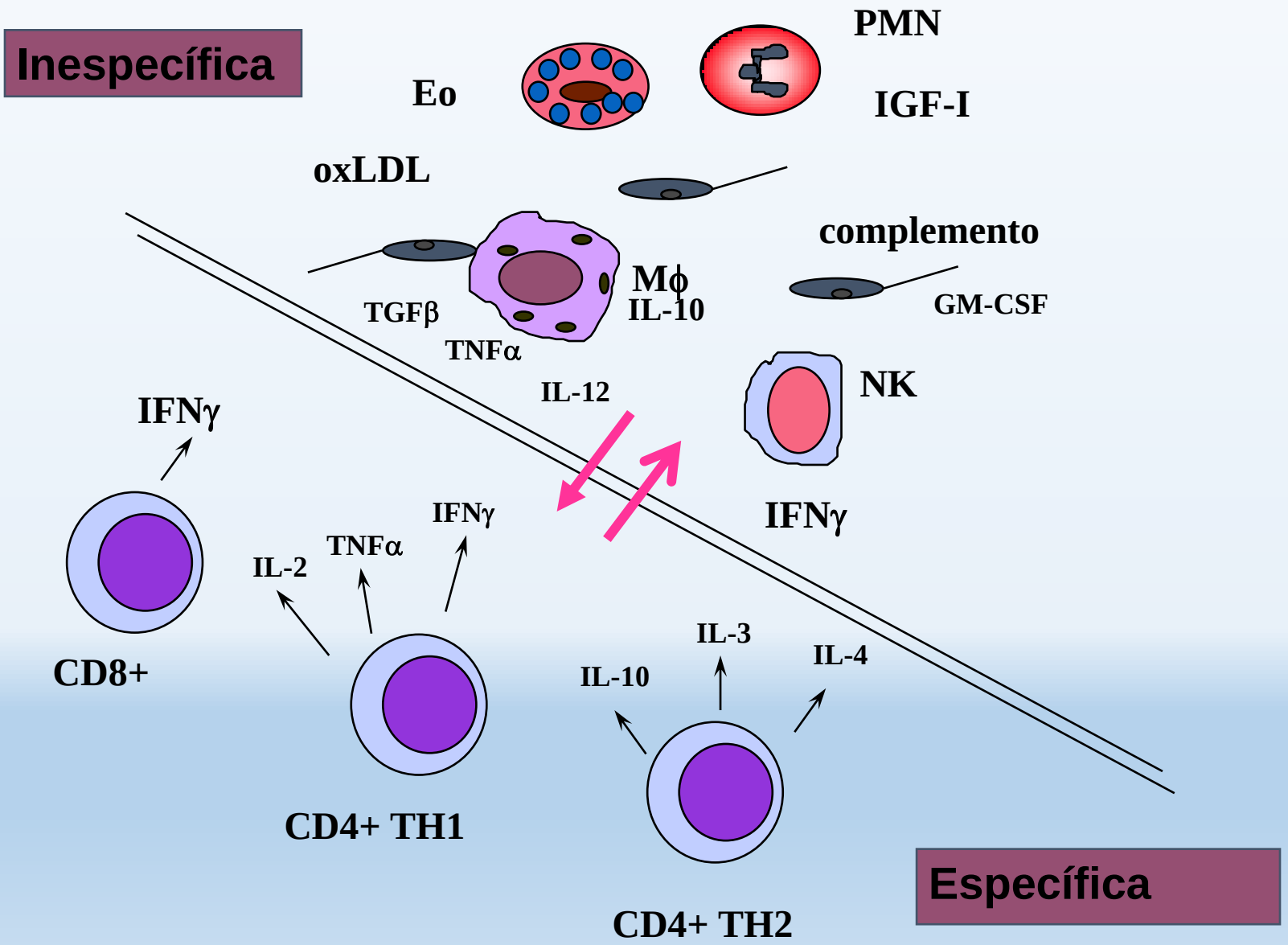
ou

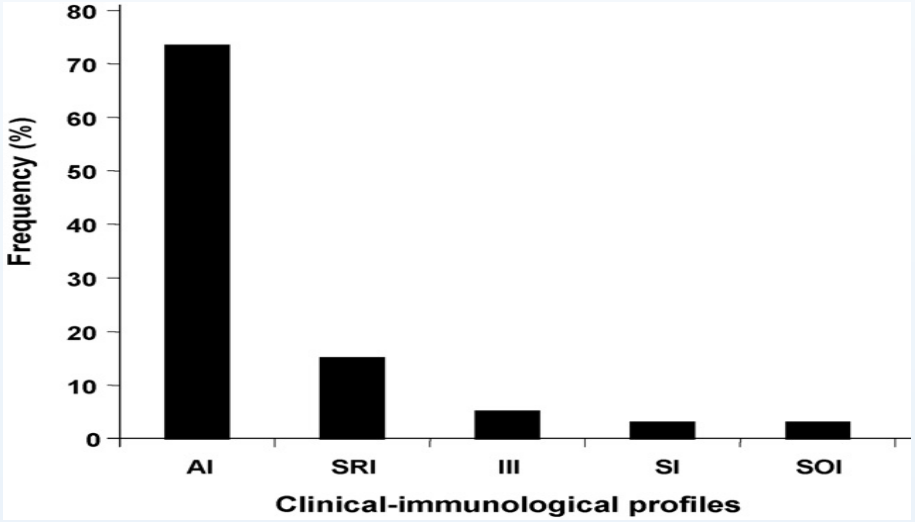


Forma visceral



Forma Cutânea atípica


Inespecífica
Eo
PMN
IGF-I
oxLDL
complemento
Mϕ
IL-10
TGFβ
TNFα
GM-CSF
NK
IL-12
IFNγ
IFNγ
IFNγ
TNFα
IL-2
CD8+
CD4+ TH1
IL-3
IL-4
IL-10
CD4+ TH2
Específica



AI: asymptomatic infection=LST+/++++ and IFAT−
SRI: subclinical resistant infection= LST+/++ and IFAT+/++
III: indeterminate initial infection=LST−and IFAT+/++
SI: symptomatic infection=LST− and IFAT+++/++++
SOI: subclinical oligosymptomatic infection=LST− and IFAT+++/++++

Table 1 Clinical and immunological spectrum of human *Leishmania (L.) infantum chagasi* infection in the Amazon region, Brazil

Susceptible immunological pole		Resistant immunological pole
Symptomatic infection (AVL) LST− IFAT+++/++++	Indeterminate initial infection (III) LST− IFAT+/++	Asymptomatic infection (AI) LST+/++++ IFAT−
Subclinical oligosymptomatic infection (SOI) LST− IFAT+++/++++		Subclinical resistant infection (SRI) LST+/++ IFAT+/++

IFAT++++: 5120—10 240 (IgG); IFAT+++: 1280—2560 (IgG); IFAT++: 320—640 (IgG); IFAT+: 80—160 (IgG); IFAT−: negative reaction; LST: leishmanin skin test; LST++++: exacerbated reaction (≥16 mm); LST+++: strong reaction (13—15 mm); LST++: moderate reaction (9—12 mm); LST+: weak reaction (5—8 mm); LST−: negative reaction.

Crescente et al, AJTMH, 103, 2009

Perfil Clínico de LV

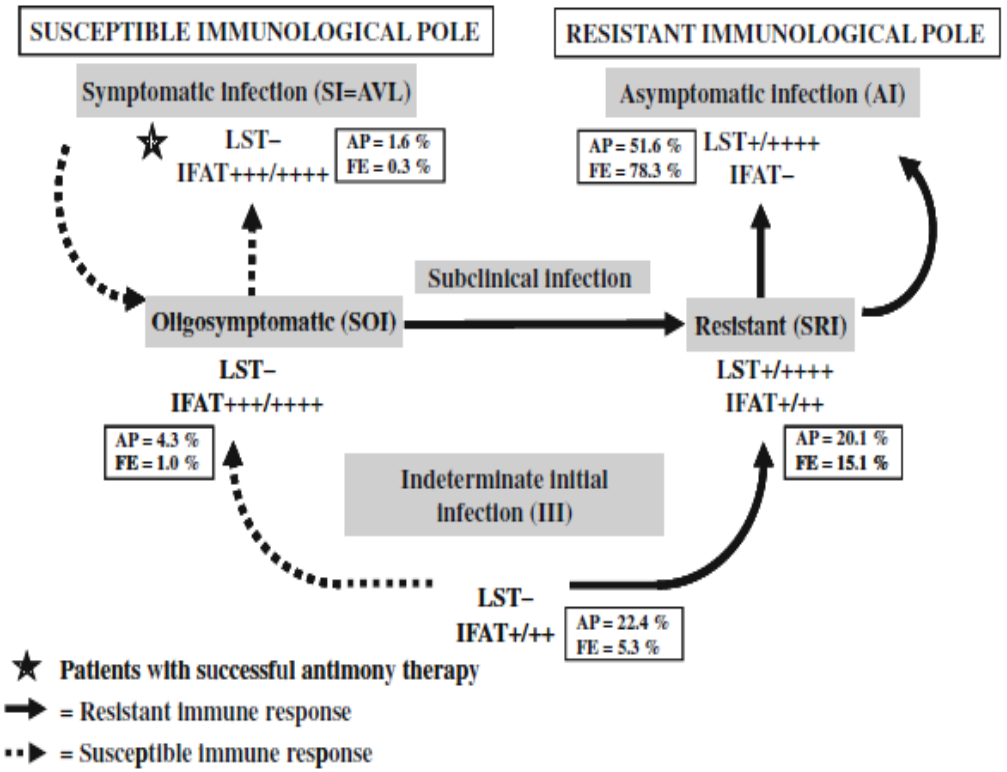


Fig. 2 Dynamics evolution of clinical-immunological profiles of human *Leishmania (L.) infantum chagasi*-infection in Amazonian Brazil. *IFAT* indirect fluorescent antibody test (IgG). *IFAT*++++ 5,120–10,240 (IgG). *IFAT*+++ 1,280–2,560 (IgG). *IFAT*++ 320–640 (IgG). *IFAT*+ 80–160 (IgG). *IFAT*– negative reaction. *LST* leishmanin skin test. *LST*++++ exacerbate reaction (≥16 mm). *LST*+++ strong reaction (13–15 mm). *LST*++ moderate reaction (9–12 mm). *LST*+ weak reaction (5–8 mm). *LST*– negative reaction. *AI* asymptomatic infection. *SI* symptomatic infection (=*AVL*). *SOI* sub-clinical oligo-symptomatic infection. *SRI* sub-clinical resistant infection. *III* indeterminate initial infection. *AP* accumulated prevalence. *FE* final evolution of infection

Silveira et al Parasitol Res (2010) 106:377–386

Interleukin-2 as a marker for detecting asymptomatic individuals in areas where *Leishmania infantum* is endemic

A.V. Ibarra-Meneses [1], E. Carrillo [1,*], C. Sánchez [1], J. García-Martínez [2], D. López Lacomba [2], J.V. San Martin [3], F. Alves [4], J. Alvar [4], J. Moreno [1]

Clinical Microbiology and Infection xxx (2016) 1.e1–1.e4

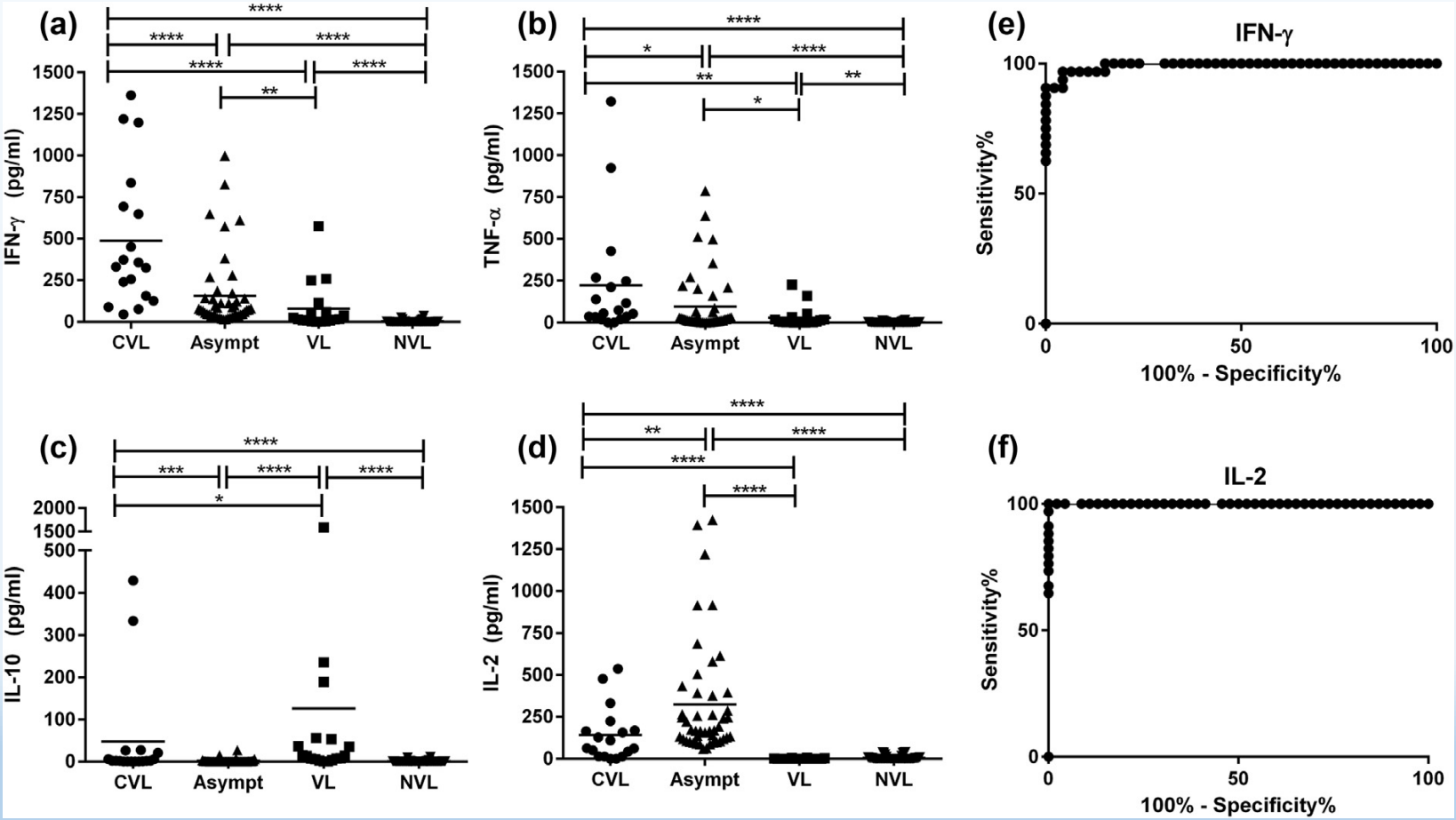
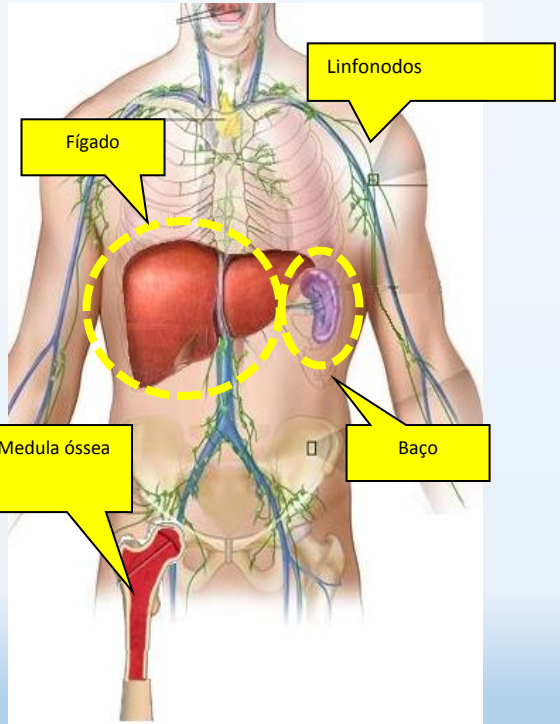


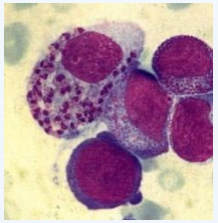
Fig. 1. Cytokine production in whole blood in response to soluble Leishmania antigen (SLA) stimulation for 24 h. (aed) Production of (a) interferon-g (IFN-g), (b) tumour necrosis factor-a (TNF-a), (c) interleukin-10 (IL-10) and (d) IL-2 in plasma following 24 h of SLA stimulation of whole blood from patients with cured visceral leishmaniasis (VL) patients (CVL; n ¼ 18), asymptomatic participants (Asympt; n ¼ 47), patients with active disease (VL; n ¼ 18), and negative controls (NVL; n ¼ 50). Horizontal bars represent the mean concentration for each cytokine. Data were analysed using the ManneWhitney U test. *p 0.05, **p 0.01, ***p 0.001, ****p 0.0001. (e,f) Receiver operating characteristic curve analysis to determine the sensitivity and specificity of IFN-g and IL-2 to detect asymptomatic participants.

Aspectos imunopatogênicos da leishmaniose visceral

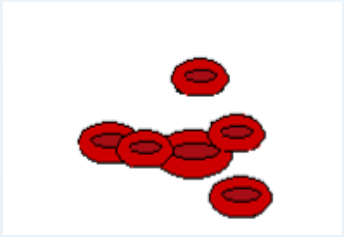
Órgãos alvo



Infecção de células do sistema reticulo endotelial

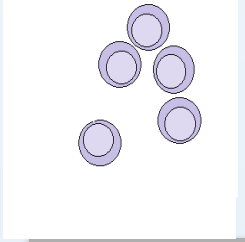


Comprometimento da medula óssea e desvio na produção de outros tipos celulares



Hemácias

Plaquetas



Neutrófilos

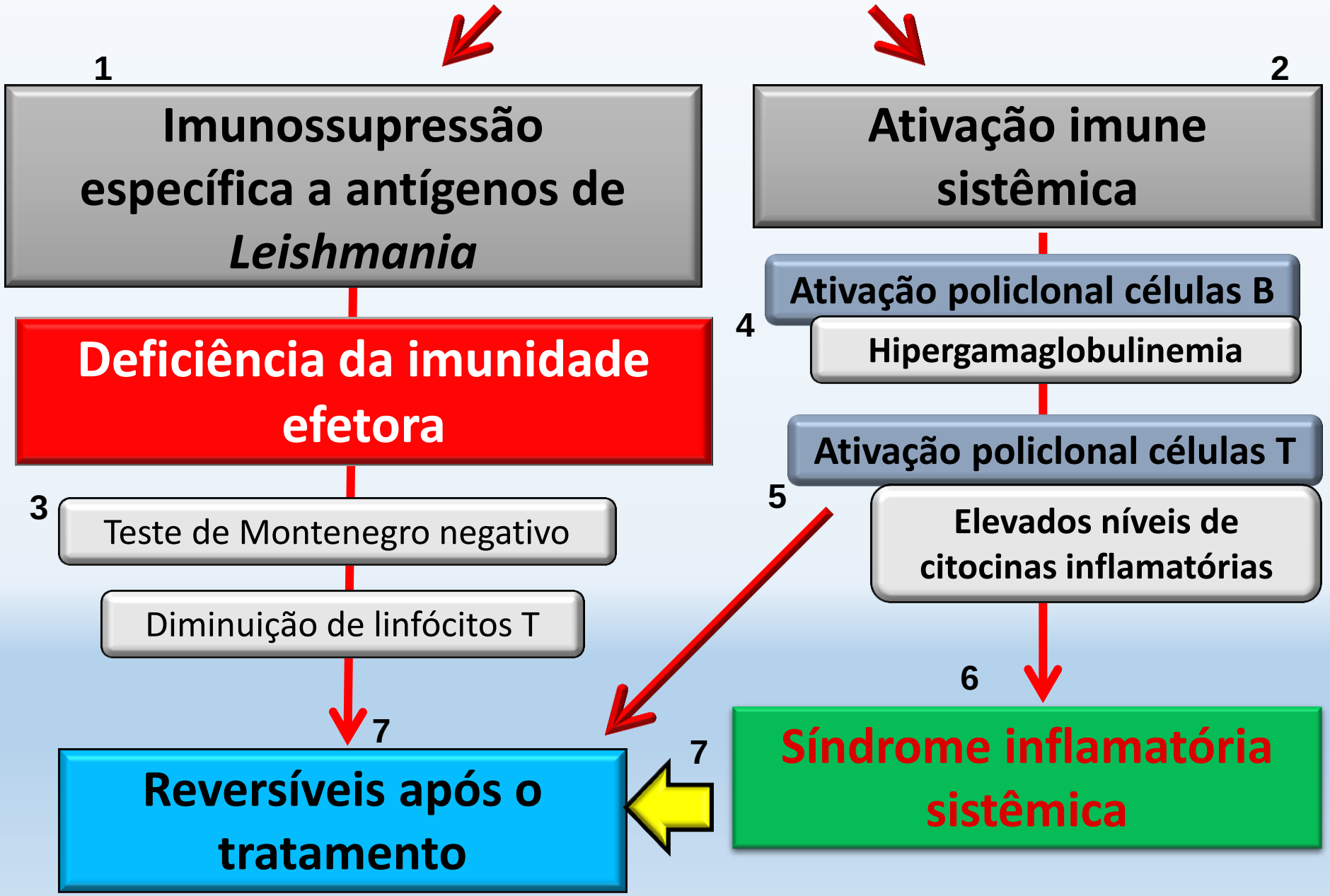
Monócitos

Alterações laboratoriais:
- ✓ Anemia
- ✓ Plaquetopenia
- ✓ Neutropenia
- ✓ Linfopenia

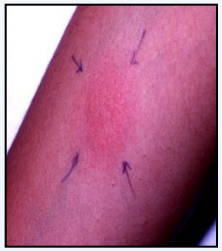
Triade clássica
- ✓Febre
- ✓Emagrecimento
- ✓Hepatoesplenomegalia

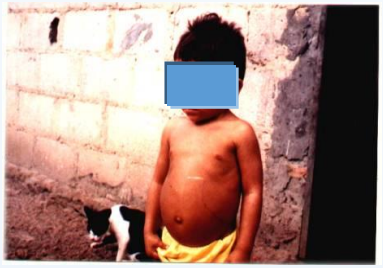
Diminuição na produção dos progenitores dos linfócitos T

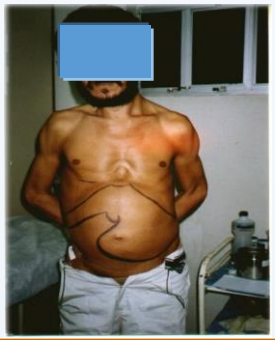
Comprometimento do sistema imune



Leishmaniose Visceral







Assintomática	Oligossintomática	Clássica

Sorologia

+	++	++++

Teste de Montenegro

+	+ ou -	-

Hepatoesplenomegalia

Ausente	Discreta	Volumosa

Para-Kalazar-Dermal Leishmaniasis

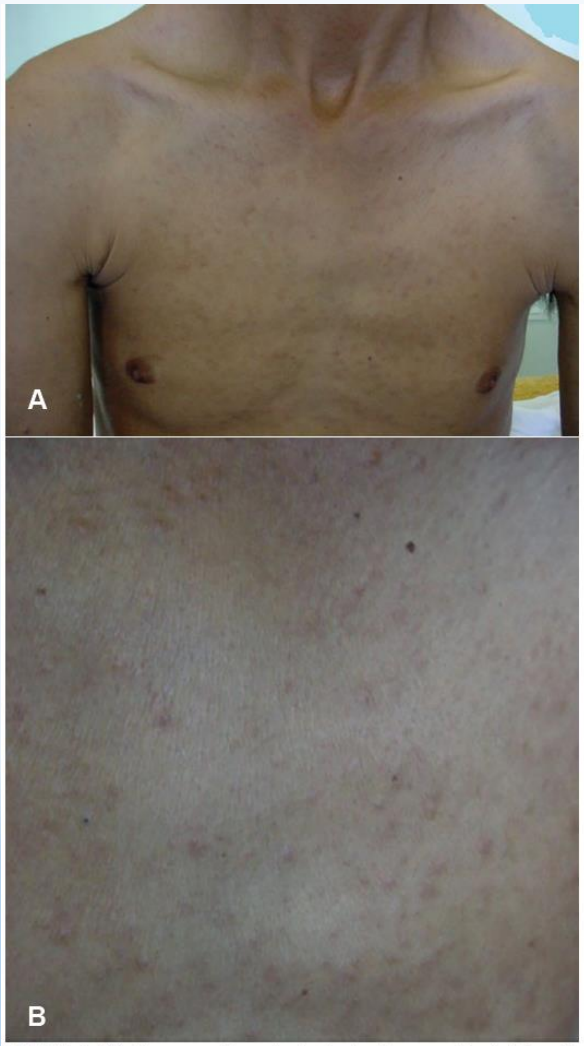


FIGURE 1: (A): Presence of papules in the trunk, caused by *Leishmania infantum*, on a patient who presented with visceral leishmaniasis. **(B):** Details of the lesions (papules) in the trunk.

Para-kala-azar dermal leishmaniasis in a patient in Brazil: a case report

Med Trop

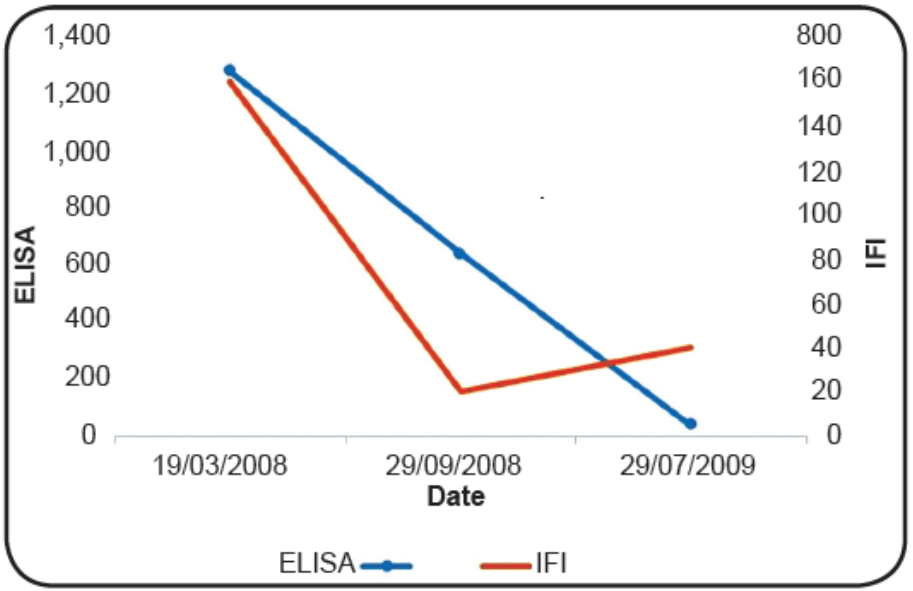


FIGURE 2: Level of anti-*Leishmania* antibodies measured using an enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IFI), using total *Leishmania* major-like antigens, during active disease, and 6 and 16 months after treatment.

American Visceral Leishmaniasis: Factors Associated with Lethality in the State of São Paulo, Brazil

Table 3: Statistical analysis of factors associated with VL lethality, state of Sao Paulo, 1999–2005 (bivariate analysis).

Features	Outcome ($n = 376$)			OR (95% CI)	P value
	Death $n = 53$	Cured $n = 323$	Total $n = 376$		
Signs and symptoms					
Asthenia	44	191	235	3.38 (1.59–7.16)	0.0008
Cardiac abnormality	9	10	19	6.53 (2.28–18.65)	<0.0001
Dehydration	12	8	20	12.11 (4.66–31.47)	<0.0001
Diarrhea	20	52	72	3.16 (1.68–5.93)	0.0002
Dyspnea	12	22	34	4.00 (1.84–8.69)	0.0001
Edema	10	11	21	6.75 (2.7–16.86)	<0.0001
Hemorrhagic manifestation	18	22	40	7.24 (3.54–14.83)	<0.0001
Jaundice	10	6	16	12.88 (4.45–37.31)	<0.0001
Pallor	39	199	238	2.02 (1.02–4.01)	0.040
Dry Cough	29	127	156	1.86 (1.04–3.35)	0.035
Vomiting	13	35	48	2.67 (1.30–5.48)	0.006
Drowsiness	9	11	20	5.8 (2.27–14.79)	<0.0001
Laboratory analysis					
Total bilirubin ≥ 2.0	13	6	19	17.17 (6.18–47.7)	<0.0001
Hypoalbuminemia ≤ 3.0	15	37	52	3.05 (1.53–6.07)	0.0009
Thrombocytopenia ≤ 100.000	31	108	139	2.8 (1.55–5.08)	0.0004
Aspartate aminotransferase > 40	20	62	82	2.55 (1.37–4.74)	0.002
Comorbidities					
Liver disease	3	2	5	9.79 (1.59–60.11)	0.020
Diabetes	5	4	9	8.46 (2.19–32.62)	0.003
Peripheral vascular disease	7	5	12	9.86 (3.0–32.4)	<0.0001
Splenectomy	2	0	2	undefined	0.019
Congestive heart failure	4	2	6	13.33 (2.38–74.78)	0.004
Use of immunosuppressive drugs	3	0	3	undefined	0.002
Tuberculosis	3	1	4	19.65 (2.0–192.74)	0.009
Fever					
≥60 days	13	26	39	3.71 (1.76–7.80)	0.0002
≥30 days	26	79	105	2.97 (1.64–5.39)	0.0002
Age					
≥30 years	36	73	109	7.25 (3.85–13.66)	<0.0001
≥50 years	28	17	45	20.16 (9.74–41.73)	<0.0001
Complications	53	64	117	undefined	<0.0001
Opportunistic infections	21	43	64	4.27 (2.26–8.08)	<0.0001
Pneumonia	13	29	42	0.40 (0.18–0.89)	0.023
Bleeding	24	2	26	26.1 (5.77–117.78)	<0.0001
Sepsis	28	0	28	undefined	<0.0001
Antimicrobial use	34	59	93	8.71 (4.56–16.64)	<0.0001
Blood derivatives	36	95	131	5.61 (2.93–10.72)	<0.0001

Madalosso et al, Jounal of Trop. Med, 2012

American Visceral Leishmaniasis: Factors Associated with Lethality in the State of São Paulo, Brazil

Table 4: Final model of factors associated with VL lethality, state of Sao Paulo, 1999–2005 (multivariate analysis).

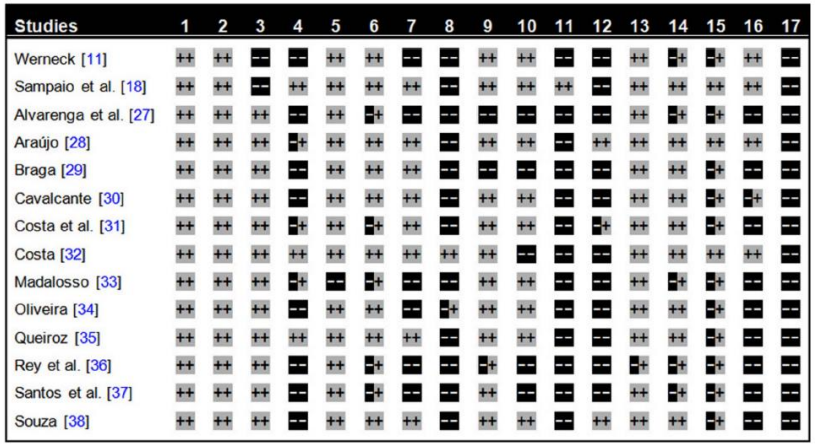
Variable	Clinical outcome			OR (95% CI)*	*P* value**
	Death $n = 53$	Cured $n = 323$	Total $n = 376$		
High total bilirubin					
Total Bilirubin ≥ 2.0 g/dL	13	6	19	7.36 (1.65–32.76)	<0.0001
Severe anemia					
Hemoglobin ≤ 5.0 g/dL	7	13	20	4.56 (1.17–17.48)	<0.0001
Antimicrobial agents	34	59	93	5.76 (2.27–14.64)	<0.0001
Age ≥ 50 years	28	17	45	29.54 (10.6–82.6)	
Length of illness (days)					
Fever >60 days	13	26	39	6.23 (2.05–18.92)	<0.0001
Hemorrhagic manifestations	18	22	40	2.62 (0.93–7.4)	0.0001
Cardiac abnormality	9	10	19	4.73 (1.3–17.23)	<0.0001
Diarrhea	20	52	72	2.76 (1.03–7.43)	<0.0001

*Odds ratio (95% confidence interval). **Likelihood ratio.

Madalosso et al, Jounal of Trop. Med, 2012

Risk Factors for Adverse Prognosis and Death in American Visceral Leishmaniasis: A Meta-analysis

1. Inclusion and exclusion criteria and selection of study population
2. Definition of VL cases selected to the study
3. Description of the treatment received by patients
4. Procedures for dealing with missing information in the medical records or in the SINAN, or losses/refusals of participants, in prospective studies
5. Measurement/confirmation of variables at the time of admission to hospital
6. Definition of variables
7. Methods of extraction of data from medical records or of measurement of variables performed in prospective studies
8. Criteria for analysis of continuous variables
9. Control of confounding factors or discriminant analysis
10. Methods of selection of variables in regression models or in discriminant analysis
11. Testing of interaction effects
12. Multicollinearity testing
13. Observance of the premises in statistical analysis
14. Description of the results (non-restriction to *P* values and/or to significant variables)
15. Sample size
16. Calibration and discrimination
17. External validation of predictive regression models



Methods/Principal Findings: The full texts of 14 studies conforming to the inclusion criteria were analyzed and their methodological quality examined by means of a tool developed in the light of current research tools. Information regarding prognostic variables was synthesized using meta-analysis. Variables were grouped according to the strength of evidence considering summary measures, patterns and heterogeneity of effect-sizes, and the results of multivariate analyses. The strongest predictors identified in this review were jaundice, thrombocytopenia, hemorrhage, HIV coinfection, diarrhea, age <5 and age >40–50 years, severe neutropenia, dyspnoea and bacterial infections. Edema and low hemoglobin concentration were also associated with unfavorable outcomes. The main limitation identified was the absence of validation procedures for the few prognostic models developed so far.

Citation: Belo VS, Struchiner CJ, Barbosa DS, Nascimento BWL, Horta MAP, et al. (2014) Risk Factors for Adverse Prognosis and Death in American Visceral Leishmaniasis: A Meta-analysis. PLoS Negl Trop Dis 8(7): e2982. doi:10.1371/journal.pntd.0002982

Fatores Preditores de Morte: LV

Prognostic models for predicting death by kala-azar built by summing up clinical and clinical plus laboratory variables, weighed by the force of statistical association in Teresina, Brazil.

	Patients ≤ two years old		Patients > two years old	
Risk factor	**Weigh of the variable in the clinical model**	**Weigh of the variable in the clinical and laboratory model**	**Weigh of the variable in the clinical model**	**Weigh of the variable in the clinical and laboratory model**
Age				
< 12 months	1	1	-	-
> 12 months	0	-	-	-
2-15 years	-	-	0	-
15-40 years	-	-	2	-
>40 years	-	-	3	-
Bleeding				
1-2 sites	1	1	-	-
3-4 sites	2	2	-	
5-6 sites	4	4	3	-
AIDS	-	-	2	2
Edema	2	2	1	-
Vomiting	-	-	1	-
Jaundice	1	-	1	1
Dyspnea	1	1	1	1
Bacterial infection	-	-	1	1
Leukocytes < 1,500/mm^3	-	-	-	1
Platelets < 50,000/mm^3	-	-	-	2
Renal failure[1]	-	-	-	2
AST or ALT > 100UK/L	-	3	-	-
Maximum score	9	11	13	10

AST: aspartate aminotransferase; **ALT**: alanine aminotransferase. [1]Glomerular filtration rate <60mL/min/m^2 or creatinine above the levels for age.

High levels of T lymphocyte activation in *Leishmania*-HIV-1 co-infected individuals despite low HIV viral load

Joanna R Santos-Oliveira[1], Carmem BW Giacoia-Gripp[2], Priscilla Alexandrino de Oliveira[3], Valdir S Amato[4], Jose Ângelo L Lindoso[5], Hiro Goto[5], Manoel P Oliveira-Neto[6], Marise S Mattos[6], Beatriz Grinsztejn[6], Mariza G Morgado[2], Alda M Da-Cruz[1*]

BMC Infectious Diseases 2010, **10**:358

Table 1 Clinical and laboratorial characteristics of HIV-1 co-infected leishmaniasis patients and control groups

Parameters	AVL/HIV-1 patients (n = 9)	ATL/HIV-1 patients (n = 8)	HIV-1 infected* (n = 16)	Healthy subjects (n = 8)
Age, years, (median)	38 (35-50)[a]	44 (38-54)[b]	39 (33-49)[c]	26 (25-30)[abc]
Male sex, n, (%)	9 (100)[d]	8 (100)[e]	15 (94)[f]	4 (50)[def]
CD4+T Cell count, cells/mm^3	62 (52-127)[g]	404 (294-597)[h]	380 (223-450)[i]	1,106 (957-1,300)[ghi]
Current AIDS diagnosis, Number of cases (%)	9 (100)	6 (75)	8 (50)	——
Time of clinical remission of leishmaniasis, months	8 (6-12)	11 (7.5-14)	——	——
Patients with undetectable viremia, (%)	5 (55.6)	4 (50)	9 (56.2)	——
Viral load levels of patients with detectable viremia, copies/mL	142,240 (24,025-279,321)	6,200 (2,012-78,176)	12,010 (2,000-136,625)	——

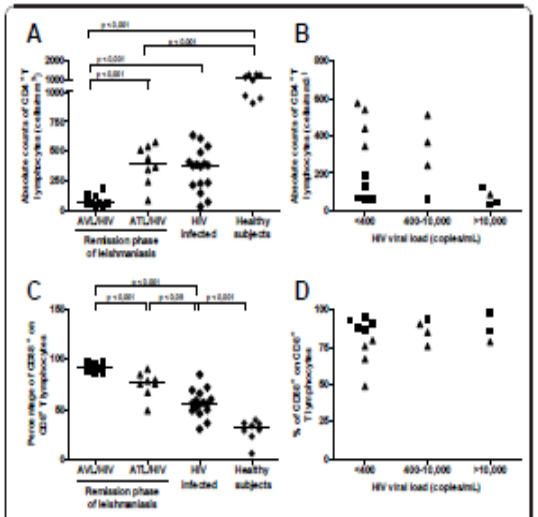


Figure 1 Relationship between lymphocyte immune status and plasmatic HIV-1 viral load in *Leishmania*/HIV-1 co-infected patients during remission phase of leishmaniasis. **A.** Absolute counts of CD4+ T lymphocytes. **B.** Absolute counts of CD4+ T lymphocytes and viral load levels. **C.** Levels of CD38 expression on CD8+ T lymphocytes. **D.** CD38 expression on CD8+ T lymphocytes and viral load levels. American visceral leishmaniasis (AVL)/HIV-AIDS patients (solid squares), American tegumentary leishmaniasis (ATL)/HIV-AIDS patients (solid triangles), HIV-1 infected adults without leishmaniasis (HIV infected, solid diamonds) and healthy subjects (solid circles). Each point represents one subject. The horizontal bars express median.

Table 3 Multivariate linear regression analysis to evaluate the association between T cell activation (CD38+ on CD8+ T lymphocytes) and independent variables in leishmaniasis and HIV-1 co-infected patients

Independent variables	Dependent variable: Percentage of CD38+ on CD8+ T lymphocytes		
	Coef[1]	SE[2]	*P*
Leishmania infection (presence or absence)	24.88	4.63	0.000011
CD4+ T cell count, cells/mm^3	-0.02	0.013	0.13
Viral load levels (detectable or undetectable)	4.12	4.85	0.39

1 Coef - Correlation coefficient, 2 SE - Standard error

Obs. HIV-1 infected patients were also included in this analysis.

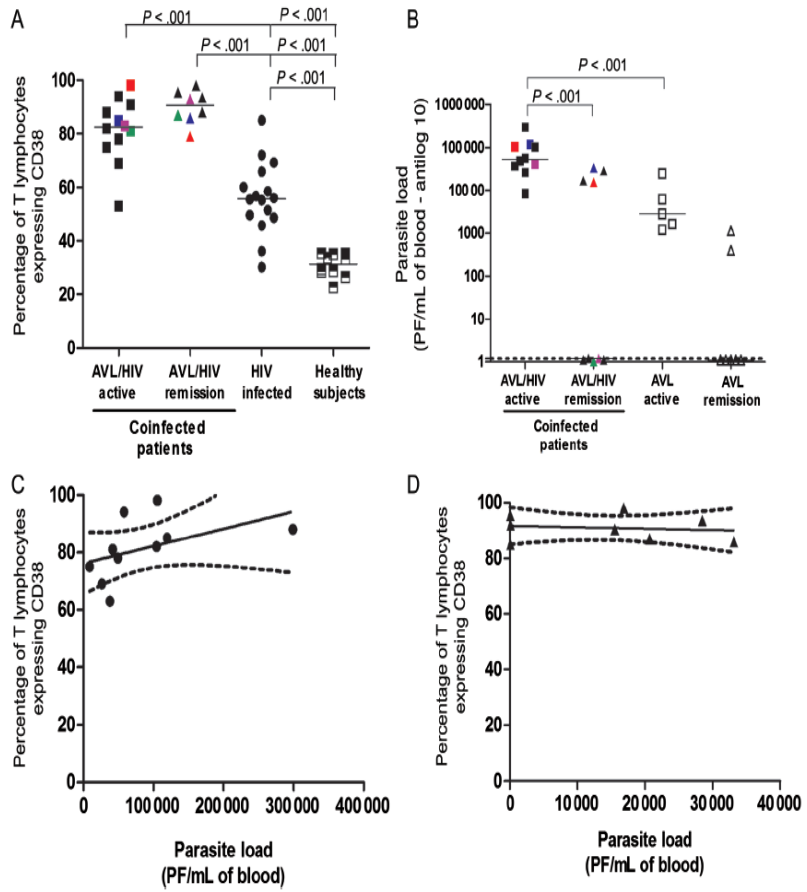
Table 2 CD4+ T cell counts and viral load levels of HIV-AIDS associated leishmaniasis patients (visceral or tegumentary) and HIV-1 infected control group

Patient's Number	CD4+ T cells counts(cells/mm^3)	Viral load levels (copies/mL)
VL/HIV-AIDS		
1	78	< 400
2	59	5,810
3	33	316,402
4	129	< 400
5	61	< 400
6	45	242,240
7	187	< 400
8	124	42,240
9	68	< 400
TL/HIV-AIDS		
1	367	1,700
2	440	< 400
3	512	2,324
4	86	146,351
5	541	< 400
6	345	< 400
7	576	< 400
8	242	10,000
HIV-1 infected		
1	146	136,625
2	543	< 400
3	215	< 400
4	34	12,010
5	230	253,761
6	609	< 400
7	391	< 400
8	491	< 400
9	377	< 400
10	73	1,750
11	371	10,000
12	236	< 400
13	635	< 400
14	382	2,000
15	394	55,239
16	410	< 400

Microbial Translocation Induces an Intense Proinflammatory Response in Patients With Visceral Leishmaniasis and HIV Type 1 Coinfection

Joanna R. Santos-Oliveira,[1] Eduardo G. Regis,[2] Carmem B. W. Giacoia-Gripp,[3] Joanna G. Valverde,[6] Priscilla Alexandrino-de-Oliveira,[7] Jose Ângelo L. Lindoso,[8] Hiro Goto,[8] Manoel P. Oliveira-Neto,[4] Jorge O. Guerra,[9] Beatriz Grinsztejn,[4] Selma B. Jerônimo,[6] Mariza G. Morgado,[3] and Alda M. Da-Cruz[1,5]

The Journal of Infectious Diseases 2013;208:57–66



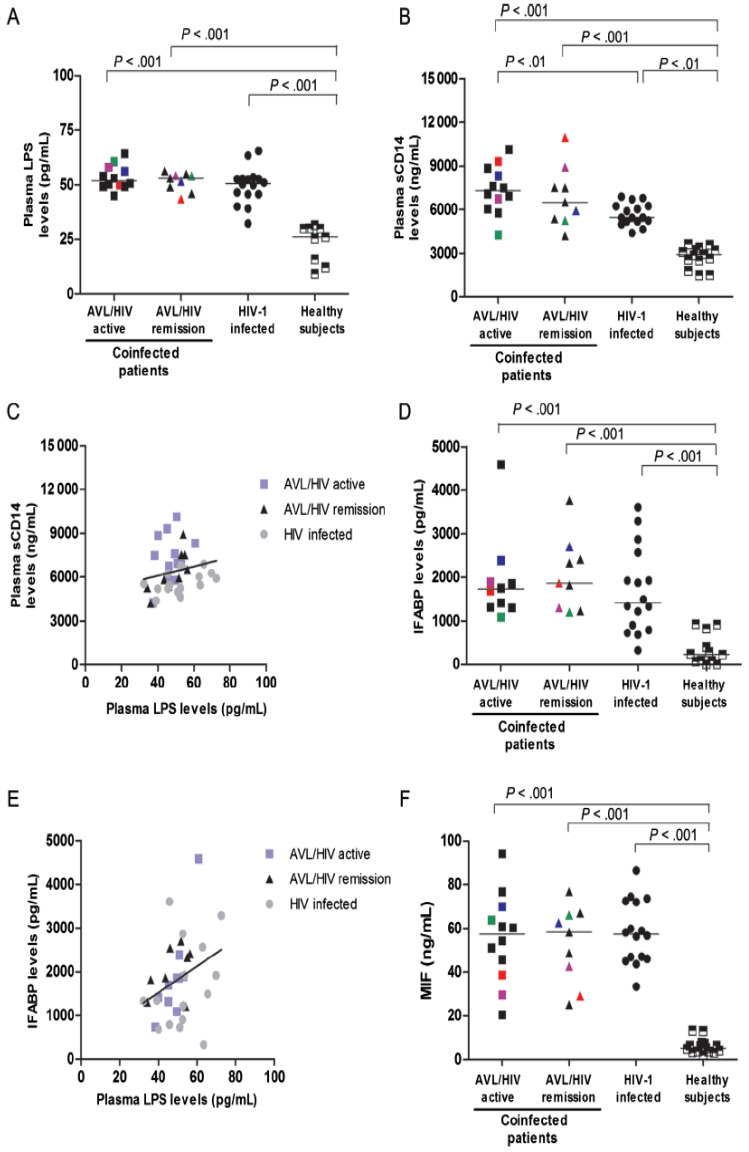


Table 1. Multivariate Analysis of Factors Associated With Cell Activation, Evaluated on the Basis of the Percentage of CD38-Positive Cells Among $CD8^+$ T Lymphocytes, Among Patients Coinfected With *Leishmania (Leishmania) infantum* and Human Immunodeficiency Virus Type 1 (HIV) and Those With HIV Infection Only

	Percentage of $CD38^+$ Cells Among $CD8^+$ T lymphocytes		
Variable	Correlation Coefficient[a]	Standard Error	*P*
$CD4^+$ T-cell count (cells/mm^3)	−0.021	0.014	.875
Viral load (copies/mL)	0.049	0.001	.624
Leishmaniasis (presence or absence)	0.817	5.478	.0001
LPS level (pg/mL)	0.373	0213	.001
sCD14 level (pg/mL)	0.061	0.002	.609
IFABP level (pg/mL)	0.153	0.002	.097
MIF level (ng/mL)	0.124	0.118	.218

Table 3. Multivariate Analysis of the Association Between Proinflammatory Cytokine Levels and Viral Load, Lipopolysaccharide (LPS) Level, Soluble CD14 (sCD14) Level, and *Leishmania* Infection Among Patients Coinfected With *Leishmania (Leishmania) infantum* and Human Immunodeficiency Virus Type 1 (HIV) and Those With HIV Infection Only

Variable	LPS Level, *P*	Viral Load, *P*	sCD14 Level, *P*	*Leishmania* Infection, *P*
TNF level	.296	.709	.980	.003
IL-1β level	.685	.766	.979	.122
IL-6 level	.018	.849	.527	.005
IL-8 level	.008	.968	.019	.001
IL-17 level	.939	.856	.246	.001
MIP-1β level	.968	.563	.011	.001
MIF level	.141	.399	.877	.969

Abbreviations: IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; IL-17, interleukin 17; LPS, lipopolysaccharide; MIF, macrophage migration inhibitory factor; MIP-1β, macrophage inflammatory protein 1β; TNF, tumor necrosis factor.

Table 2. Plasma Proinflammatory Cytokine Levels in the Study Population

Cytokine	Active AVL/HIV (n = 5)	Remission AVL/HIV (n = 7)	HIV Infected	Active AVL (n = 5)	Remission AVL (n = 7)	Healthy Subjects (n = 8)	P^a	P^b	P^c	P^d
IFN-γ	2795 (1344–7104)	2411 (1415–6157)	150 (56–332)	1143 (445–4446)	783 (367–3482)	19 (5.3–145)	.0001	.0001	.126	.05
TNF	490 (284–1503)	374 (302–1207)	165 (86–200)	143.5 (37.7–555)	100 (57.3–588.5)	2 (1.5–8.5)	.0001	.001	.05	.07
IL-6	536 (61–6128)	947 (276–9068)	81 (45–110)	416 (211–557)	49 (30–115)	1 (0.3–2.5)	.0001	.006	.47	.04
IL-8	2447 (1050–10 844)	3244 (2439–17 999)	170 (130–220)	8000 (1887–13 578)	4325 (427–8988)	2.5 (1.5–3.0)	.01	.006	.536	.445
IL-1β	16 (3.5–209)	112.5 (17.1–351)	15 (10–20)	9.7 (4–226)	7.5 (2–138)	0.5 (0.4–0.62)	.01	.0001	.958	.05
IL-17	231 (118–417)	256 (161–500)	65.2 (46–90)	288 (102–398)	193.5 (131–626.6)	2 (2–16)	.0008	.0006	.874	.837
MIP-1β	2157 (430–3928)	546 (441–923)	243 (165–318)	730.3 (418–3363)	571.5 (426–1111)	14.3 (0.1–50.2)	.008	.008	.924	.571

Microbial Translocation Induces an Intense Proinflammatory Response in Patients With Visceral Leishmaniasis and HIV Type 1 Coinfection

Joanna R. Santos-Oliveira,[1] Eduardo G. Regis,[2] Carmem B. W. Giacoia-Gripp,[3] Joanna G. Valverde,[6] Priscilla Alexandrino-de-Oliveira,[7] Jose Ângelo L. Lindoso,[8] Hiro Goto,[8] Manoel P. Oliveira-Neto,[4] Jorge O. Guerra,[9] Beatriz Grinsztejn,[4] Selma B. Jerônimo,[6] Mariza G. Morgado,[3] and Alda M. Da-Cruz[1,5]

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Conclusions. LPS levels along with the immune consequences of *Leishmania* infection were associated with elevated cellular activation in coinfected patients. As a consequence, secondary chemoprophylaxis for leishmaniasis or even the use of antiinflammatory drugs or antibiotics may be considered for improving the prognosis of AVL/HIV.

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PLoS NEGLECTED TROPICAL DISEASES

Predictors of Visceral Leishmaniasis Relapse in HIV-Infected Patients: A Systematic Review

Gláucia F. Cota[1,3]*, Marcos R. de Sousa[2], Ana Rabello[1]

1 Post-Graduate Program in Health Sciences, René Rachou Institute, Fundação Oswaldo Cruz, Belo Horizonte, Minas Gerais, Brazil, 2 Post-Graduate Program in Adult Health Sciences, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, 3 Eduardo de Menezes Hospital, Fundação Hospitalar do Estado de Minas Gerais-FHEMIG, Belo Horizonte, Minas Gerais, Brazil

Recidiva de LV persiste alta mesmo com uso de HAART

A profilaxia secundária confere proteção parcial (67% x 31%)

São fatores relacionados com recidiva:

- CD4+ inferior a 100 cels/mL ao diagnóstico de LV;
- recuperação insuficiente de CD4+ após o tratamento;
- episódios prévios de recidiva

Visceral Leishmaniasis and HIV Coinfection in Latin America

José Angelo Lindoso[1,2,3]*, Gláucia Fernandes Cota[4,5], Alda Maria da Cruz[6,7], Hiro Goto[3,8], Ana Nilce Silveira Maia-Elkhoury[9], Gustavo Adolfo Sierra Romero[10,11,12], Márcia Leite de Sousa-Gomes[13], Joanna Reis Santos-Oliveira[6], Ana Rabello[5]* PLOSNTD.

Table 1: Studies reporting visceral leishmaniasis-HIV coinfection in the Americas, 1990-2013.

Publication year	Author	Country	Year-period	Study design
1990	Nicodemo et al.	Brazil	1989	Case report
1995	Hernadez et al.	Venezuela	1992	Case report
1999	Borges et al.	Brazil	1998	Case report
2000	Ramos-Santos et al.	Mexico	1997	Case report
2001	Chehter et al.	Brazil	1995	Case report
2002	Bittencourt et al.	Brazil	2000	Case report
2002	Orsini et al.	Brazil	1997	Case report
2002	Silva et al.	Brazil	1998	Case report
2003	Rabello et al.	Brazil	2003	Review
2008	Roselino et al.	Brazil	1995	Case report
2008	Maia-Elkhoury et al.	Brazil	2001-2005	Case series
2009	Carnaúba Jr et al.	Brazil	2004	Case report
2009	Daher et al.	Brazil	2003-2007	Case series
2010	Alexandrino-de- Oliveira et al.	Brazil	2000-2006	Case series
2010	Santos Oliveira et al.	Brazil	Unknown	Case series
2011	Nascimento et al.	Brazil	1990-2008	Case series
2011	Sousa-Gomes et al.	Brazil	2007-2008	Case series
2011	Luz et al.	Brazil, Paraguay	Unknown	Case series
2012	Santos-Oliveira et al.	Brazil	2006	Case series
2012	Cavalcanti et al.	Brazil	2008-2010	Case series
2012	Souza et al.	Brazil	2000-2005	Case series

Box 1. Five bullet points of learning.

1. There is increase of visceral/leishmaniasis coinfection in Latin America, due to overlap areas of both diseases and the profile of coinfected patients are male and adults age between 20 to 49 years. We suggest HIV testing be included as part of the routine evaluation of visceral leishmaniasis patients in Latin America, mainly in young adults.

2. The impact on the immune system caused by Leishmania and HIV infections contribute to progress of the diseases. The chronic activation caused by Leishmaniainfection can constitute an additional factor for worsening the clinical condition of HIV patients, having a consequence enhanced viral load, T –cell proliferation and cell death induced by activation. The HIV infection also impairs the Leishmania-specific T lymphocyte proliferation and IFN-gamma production, favoring the spread of Leishmania parasite.

3. Clinical presentation of visceral leishmaniasis in HIV-infected patients is similar to patients without HIV infection; however diarrhea to be common in coinfected patients and hepatomegaly appears to be less common in coinfected patients. Cutaneous lesion caused by Leishmania infantum, characterized by PKDL-like, is rare in HIV-infected patient from Latin America.

4. Regarding diagnostic of visceral leishmaniasis in HIV-infected patient, parasitological tests are more sensitive, but serological tests have variable sensitivity according to antigen and method used. Based on data from Latin America, regarding diagnostic of visceral leishmaniasis in HIV-infected patients, we suggest use parasitological test to confirm diagnostic of visceral leishmaniasis.

5. Visceral leishmaniasis in HIV-infected patient presents more relapse and lethality. The predictor of VL relapses are absence of an increase in CD4+ T cell counts at follow-up patients, a lack of prophylaxis, a previous history of visceral leishmaniasis and CD=T cell counts bellow 100 cells/mL at the time of primary VL diagnosis. Antiretroviral therapy should be initiated as soon as possible, including protease inhibitor.

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PLOS | NEGLECTED TROPICAL DISEASES

Leishmania-HIV Co-infection: Clinical Presentation and Outcomes in an Urban Area in Brazil

Gláucia F. Cota[1,2]*, Marcos R. de Sousa[3], Andrea Laender Pessoa de Mendonça[2], Allan Patrocinio[2], Luiza Siqueira Assunção[2], Sidnei Rodrigues de Faria[2], Ana Rabello[1]

Table 1. Demographic and clinical variables according to HIV infection status.

	HIV negative (%) n = 44	HIV positive (%) n = 46	p
Age (mean ± SD), years	37,1±14,0	41,0±10,9	0.13
Sex (male:female)	11:33	11:35	1.00
Previous VL episode	2/44 (4.5)	20/46 (43.5)	0.00
Malnutrition	11/44 (25.0)	28/46 (60.9)	0.00
Median length of illness (IR), days	60 (30–120)	60 (40–91)	0.14
Median spleen size# (IR), cm	6 (4–10)	5 (2–7)	0.02
Median liver size§ (IR), cm	5 (4–7)	4 (2–5)	0.01
Fever	39/44 (88.6)	28/46 (60.9)	0.00
Hepatosplenomegaly	40/44 (90.9)	31/46 (67.4)	0.01
Cytopenia	44/44 (100)	46/46 (100)	1.00
Jaundice	14/44 (31.8)	7/46 (15.2)	0.12
Edema	15/44 (34)	8/46 (17.4)	0.09
Hypotension	4/44 (9.1)	8/46 (17.4)	0.35
Bleeding	10/44 (22.7)	9/46 (19.6)	0.79
Bleeding site			0.81
Skin/Mucosa	6/44 (13.6)	4/46 (8.7)	
Digestive tract	3/44 (6.8)	4/46 (8.7)	
Urinary tract	1/44 (2.3)	1/46 (2.2)	
Dyspnea	8/44 (18.2)	8/46 (17.4)	1.00
Diarrhea	5/44 (11.4)	10/46 (21.7)	0.26
Vomiting	14/44 (31.8)	11/46 (23.9)	0.48
Median hemoglobin (IR), g/dL	8.5 (7.2–9.5)	8.2 (7.2–9.0)	0.47
Median leukocyte count (IR), cells/L	1850 (1275–2679)	2000 (1575–2800)	0.14
Median platelets count (IR), cells/L	90.000 (61500–115.000)	114.500 (82.750–173.000)	0.00
Median total bilirubin (IR), mg%	0.9 (0.6–1.55)	0.6 (0.5–1.1)	0.23
GOT (IR), IU/L	79 (40.5–155)	44 (27.2–61.7)	0.00
Serum creatinine (IR), mg%	0.9 (0.7–1.1)	0.8 (0.7–1.1)	0.25
RNI (IR)	1.3 (1.2–1.4)	1.3 (1–1.5)	0.61
Serum albumin (IR), mg%	2.6±0.6	2.7±0.7	0.62

Tratamento da LV

Tratamento da Leishmaniose Visceral

- **Antimonial pentavalente:**
  - **N-metil glucamina: Glucantime**
  - **Estibogluconato de sódio: Pentostan**
- **Anfotericina B**
  - Desoxicolato: ???
  - Lipossomal
- **Miltefosine**
  - **Kalazar Indiano**

REVISÃO SISTEMÁTICA: TRATAMENTO DA LV HUMANA NA AMÉRICA LATINA

Country	Type of study	Number of subjects	Mean patient age (years)	Treatment interventions	Dose and route	Follow-up period	Outcomes (%)	Ref.
Brazil	Open-label	10	20.0	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 10 d. I.V.	6–12 months	Cure 10/10 (100)	[90]
Brazil	Open-label	10	19.0	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 7 d. I.V.	6–12 months	Cure 10/10 (100)	[90]
Brazil	Open-label	10	16.5	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 5 d. I.V.	12 months	Cure 9/10 (90)	[91]
							Relapse 1/10 (10)	
Brazil	Open-label Phase II	13	7.6	Liposomal amphotericin B	14mg/kg (total) . I.V.	6 months	Cure 8/13 (61)	[86]
							Failure 1/13 (8)	
							Relapse 4/13 (31)	
Brazil	Open-label Phase II	4	7.5	Liposomal amphotericin B	10mg/kg (total) I.V.	6 months	Cure 4/4 (100)	[86]
Brazil	Open-label Phase II	15	10.1	Liposomal amphotericin B	20mg/kg (total) I.V.	6 months	Cure 13/15 (87)	[86]
							Relapse 2/15 (13)	
Brazil	Open-label, dose-escalating trial	4	19.0	WR6026 (sitamaquine)	1.0mg/kg/d for 28 d. Oral.	12 months	Cure 0/4 (0)	[89]
Brazil	Open-label, dose-escalating trial	6	32.8	WR6026 (sitamaquine)	1.5mg/kg/d for 28 d. Oral	12 months	Cure 1/6 (17)	[89]
Brazil	Open-label, dose-escalating trial	6	23.8	WR6026 (sitamaquine)	2.0mg/kg/d for 28 d. Oral.	12 months	Cure 4/6 (67)	[89]
Brazil	Open-label, dose-escalating trial	5	23.8	WR6026 (sitamaquine)	2.5mg/kg/d for 28 d. Oral	12 months	Cure 1/5 (20)	[89]
Brazil	Open-label, dose-escalating trial	1	22.0	WR6026 (sitamaquine)	3.25mg/kg/d for 28 d. Oral	12 months	Cure 0/1 (0)	[89]

Romero and Boelaert, PLOS , 2010

Efficacy and safety of available treatments for visceral leishmaniasis in Brazil: A multicenter, randomized, open label trial

Gustavo Adolfo Sierra Romero[1]*, Dorcas Lamounier Costa[2], Carlos Henrique Nery Costa[2], Roque Pacheco de Almeida[3], Enaldo Viera de Melo[3], Sílvio Fernando Guimarães de Carvalho[4], Ana Rabello[5], Andréa Lucchesi de Carvalho[6], Anastácio de Queiroz Sousa[7], Robério Dias Leite[7], Simone Soares Lima[8], Thais Alves Amaral[9], Fabiana Piovesan Alves[10], Joelle Rode[11], the Collaborative LVBrasil Group[¶]

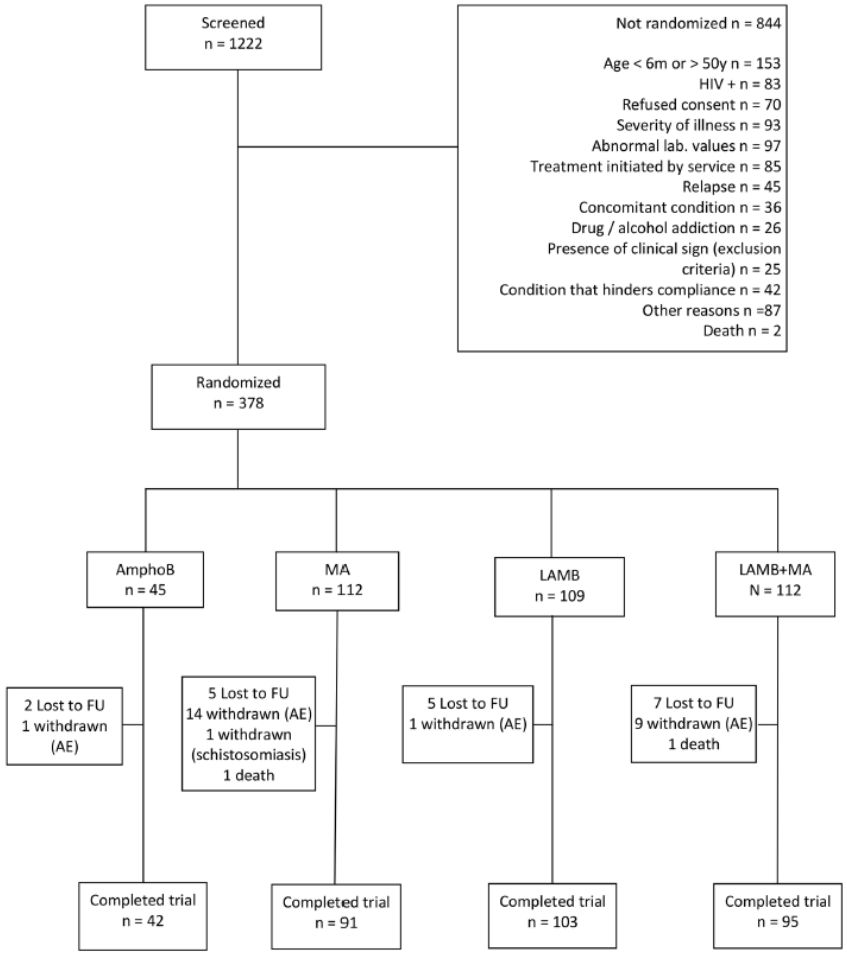


Fig 1. CONSORT patient flowchart. Flow diagram of the progress through the phases of the trial. AmphoB = amphotericin B deoxycholate; MA = meglumine antimoniate; LAMB = Liposomal amphotericin B.

Table 1. Baseline demographic, clinical and laboratory characteristics of 332 participants effectively randomized to the three remaining arms of the trial.

Characteristics	MA n = 111	LAMB n = 109	LAMB + MA n = 112
Demographic			
Age (median, years)	4.77	4.36	3.36
Percentile 25 and 75	(2.05–10.37)	(2.13–10.27)	(1.84–9.19)
Interval	(0.61 to 47.61)	(0.56 to 48.64)	(0.49 to 48.83)
Male			
% (n)	58.6 (65/111)	54.1 (59/109)	52.7 (59/112)
Time of exposure in endemic area (median, years)	4.42 (n = 110)	3.96 (n = 108)	3.17 (n = 111)
Percentile 25 and 75	(1.83–9.94)	(1.88–8.92)	(1.75–8.00)
Interval	(0.25 to 42.92)	(0.42 to 48.67)	(0.50 to 44.08)
Time of illness evolution (median, months)	1.0	1.0 (n = 108)	0.80
Percentile 25 and 75	(0.5–2.0)	(0.5–2.0)	(0.5–2.0)
Interval	(0.16 to 30.0)	(0.23 to 13.0)	(0.16 to 12.00)
Physical exam			
Weight (median, kg)	16.7	15.2	15.0
Percentile 25 and 75	(12.0–28.5)	(11.6–29.4)	(10.8–30.6)
Interval	(2.0 to 84.7)	(6.5 to 76.0)	(5.8 to 79.0)
Splenomegaly			
% (n)	98.2 (109/111)	100 (109/109)	100 (112/112)
Spleen size below the left costal margin (median, cm)	6.5 (n = 109)	7.0 (n = 108)	7.0 (n = 107)
Percentile 25 and 75	(5.0–10.0)	(5.0–10.0)	(5.0–9.0)
Interval	(0.0 to 25.0)	(1.0 to 18.0)	(2.0 to 23.0)
Hepatomegaly			
% (n)	99.1 (110/111)	94.5 (103/109)	97.3 (109/112)
Liver size below the right costal margin (median, cm)	4.0	4.0 (n = 108)	4.0 (n = 109)
Percentile 25 and 75	(3.0–6.0)	(3.0–6.0)	(3.0–6.0)
Interval	(0.0 to 16.0)	(0.0 to 11.0)	(0.0 to 11.0)
Bleeding			
% (n)	2.7 (3/111)	2.8 (3/109)	0.9 (1/112)
Edema			
% (n)	9.9 (11/111)	6.4 (7/109)	7.1 (8/112)
VL diagnosis tests			
rK39 rapid test positivity			
% (n)	92.8 (103/111)	94.5 (103/109)	93.7 (104/111)
Positive direct examination for parasite in bone marrow smear			
% (n)	64.9 (61/94)	66.7 (60/90)	54.5 (54/99)
Positive culture of bone marrow aspirate			
% (n)	48.9 (45/92)	44.4 (40/90)	48.4 (45/93)
Bacterial cultures			
Positive blood culture			
% (n)	6.5 (7/108)	1.9 (2/107)	10.4 (11/106)
Positive urine culture			
% (n)	5.1 (5/98)	5.5 (5/91)	9.8 (9/92)
Complete Blood Count			
Leukocytes count/uL	2970	2880	2870
Percentile 25 and 75	(2000–4030)	(1990–4500)	(1880–3982)
Interval	(760 to 11300)	(880 to 12660)	(1000 to 9860)

PLOS Neglected Tropical Diseases June 29, 2017

Table 2. Treatment efficacy at six months follow-up as per ITT approach.

Treatment	% of participants cured (n/total)	% of participants not cured (n/total)	Difference in cure rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	77.5 (86/111)	22.5 (25/111)		
LAMB	87.2 (95/109)	12.8 (14/109)	9.7 (-0.28 to 19.68)	0.060[a]
LAMB + MA	83.9 (94/112)	16.1 (18/112)	6.4 (-3.93 to 16.73)	0.222[b]
Total	82.8 (275/332)	17.2 (57/332)		

Table 3. Treatment efficacy at six months follow-up as PP approach.

Treatment	% of participants cured (n/total)	% of participants not cured (n/total)	Difference in cure rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	94.5 (86/91)	5.5 (5/91)		
LAMB	92.2 (95/103)	7.8 (8/103)	-2.3 (-9.23 to 4.60)	0.528[a]
LAMB+MA	98.9 (94/95)	1.1 (1/95)	4.4 (-0.73 to 9.53)	0.112[b]
Total	95.1 (275/289)	4.9 (14/289)		

Table 4. Early withdrawal rate due to the occurrence of AE/SAE during treatment as per ITT.

Treatment	Early withdrawal rate due to occurrence of AE/SAE—% (n/total)	Difference in early withdrawal rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	13.5 (15/111)		
LAMB	0.92 (1/109)	-12.6 (-19.18 to -5.97)	<0.001[a]
LAMB+MA	8.9 (10/112)	-4.6 (-12,86 to 3,66)	0.278[b]
Total	7.8 (26/332)		

Table 3. Potential regimens of LAMB that have been developed for use against VL*.

Regimen	Cost (USD) [70]	Efficacy (phase of trial done)	Comments
LAMB i.v. 10 mg/kg single dose	126	95% (P3)	South Asia only, poor efficacy in East Africa
LAMB 20 mg/kg over 4 doses	252	98% (P4)	South Asia only and possibly Europe and Latin America, poor efficacy in East Africa
LAMB 5 mg/kg + MF 100 mg/kg/day for 8 days	88 – 109	97.5% (P3)	South Asia only; teratogenicity of MF may hinder uptake
LAMB 5 mg/kg + PM 15 mg/kg/day for 11 days	79	97.5% (P3)	South Asia only; use of daily PM injections may hinder uptake
LAMB 30 mg/kg over 6 – 10 doses	378	90% (observational field data only)	East Africa only; no clinical trial data available at this dose

*Based on data from the WHO expert committee report 2010.

LAMB: Liposomal amphotericin B (all trials here have used AmBisome™); MF: Miltefosine; PM: Paromomycin.

Tratamento específico

- Indicações de uso da anfotericina B lipossomal:

Indicações	Grau de recomendação
idade menor que 1 ano	D
idade maior que 50 anos	D
escore de gravidade: clínico > 4 ou clínico-laboratorial > 6	D
insuficiência renal	A
insuficiência hepática	D
insuficiência cardíaca	D
intervalo QT corrigido maior que 450 ms	D
uso concomitante de medicamentos que alteram o intervalo QT	D
hipersensibilidade ao antimonial pentavalente ou a outros medicamentos utilizados para o tratamento da LV	D
infecção pelo HIV	D
comorbidades que comprometem a imunidade	D
uso de medicação imunossupressora	D
falha terapêutica ao antimonial pentavalente ou a outros medicamentos utilizados para o tratamento da LV	D
gestantes	D

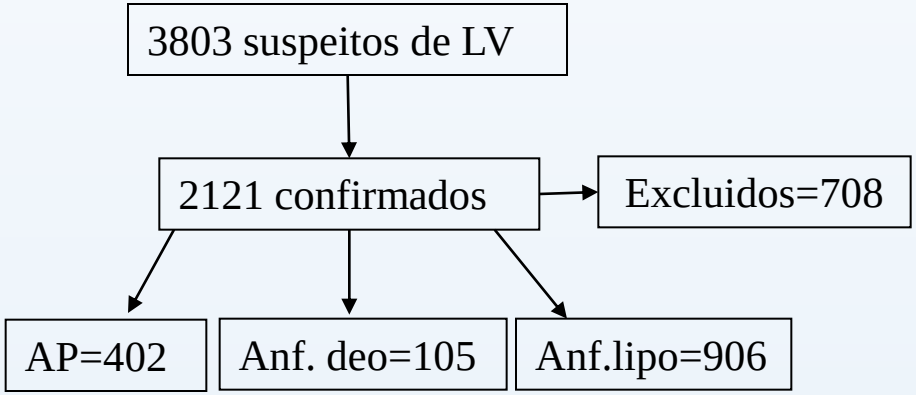
Recomendações da Anfotericina B lipossomal

- 1- Recomendação do CDC:
  - Imunocompetentes a dose de 3 mg/kg/dia, com dose total de 21 mg / kg.
  - **Para pacientes imunossuprimidos: 4 mg/kg/d com dose total de até 40 mg/kg.**
- 2- Orientação da OPAS para tratamento de pacientes com LV:
  - Dose de 3-5 mg/kg/d de anfotericina b lipossomal por 3 a 6 dias até completar 20 mg/kg de dose total.
  - Coinfectados com HIV:
    - dose recomendada é de 3-5 mg/kg/d, com dose total entre 20-40 mg/kg.
- 3- Recomendação do Ministério da Saúde
  - 3 mg/kg/dia, durante sete dias
  - 4 mg/kg/dia, durante cinco dias.
    - Taxa de recidiva:
      - 6,22%
      - Segura e eficaz para o tratamento da LV.

Tratamento LV no Estado de São Paulo

- Anfotericina b lipossomal
  - 4 mg/kg/dia por 5 días (total de 20 mg/kg)
  - 3 mg/kg/dia por 7 días (total de 21 mg/Kg)
- Antimonial pentavalente
  - 20 mg/kg/dia por 28 dias

Avaliação da resposta terapêutica da LV no estado de São Paulo: 2007 a 2015

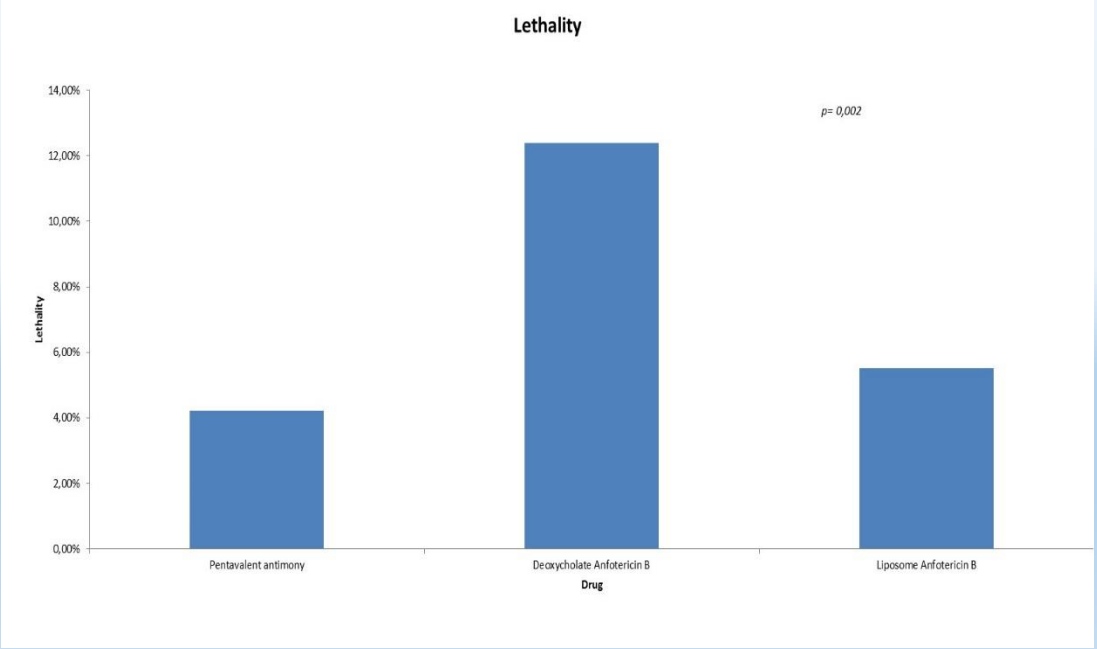


Adultos sexo masculino:
20 a 59 anos de idade

Letalidade geral=7,8%

- AP=4,23%
- **Anf deo=12,38%**
- Anf lipo=5,52%

> 60 anos



COINFECÇÃO LV-HIV/AIDS

➢ *Avaliação da resposta terapêutica*

Letalidade e recidiva nos pacientes LV e coinfectados LV-HIV/AIDS
no Estado de São Paulo (1999-2010)

DESFECHO	LV	LV-HIV/AIDS	*p* valor
Óbitos (n; %)	88/1078 (8,2)	23/95 (24,2)	< 0,001
Recidivas (n;%)	19/1078 (1,8)	10/95 (10,5)	< 0,001

Qui-quadrado ($p < 0,05$)

Queiroz-e-Silva, 2013

COINFECÇÃO LV-HIV/AIDS

➢ *Avaliação da resposta terapêutica*

Avaliação da resposta ao tratamento anti-*Leishmania* em pacientes coinfectados LV-HIV/AIDS no Estado de São Paulo (1999-2010)

DESFECHO	AP	AnBd	AnBL	*p valor
Cura No/Total (%)	25/36 (69,44)	5/12 (41,66)	30/47 (63,82)	0,223
Falhas No/Total (%)	4/36 (11,11)	2/12 (16,66)	0/47 (00,00)	0,034
Óbitos No/Total (%)	6/36 (16,66)	5/12 (41,66)	10/47 (21,27)	0,192
Recidivas No/Total (%)	1/36 (2,77)	0/12 (0,00)	7/47 (14,89)	0,076
TOTAL (%)	**36/36 (100%)**	**12/12 (100%)**	**47/47 (100%)**	

* Kruskal-Wallis One Way Analysis of Variance on Ranks ($p < 0,05$)
Tratamentos resgatados = 101. Outras drogas = 6.
AP= Antimonial Pentavalente, AnBd = Anfotericina B desoxicolato, AnBL= Anfotericina B Lipossomal

Queiroz-e-Silva, 2013

TABLE 4. Treatment recommendations for leishmaniasis in immunosuppressed individuals.

Organization	Target group	Preferred therapy	Alternative therapy
VL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Liposomal amphotericin B 21 mg/kg total dose 3 mg/kg IV days 1–5, 14, 21	Amphotericin B deoxycholate 1.0 mg/kg daily for 15–20 days or a pentavalent antimony compound[a]
Centers for Disease Prevention and Control [128]	HIV	Liposomal amphotericin B 20–60 mg/kg total dose 2–4 mg/kg IV daily or interrupted schedule (e.g. 4 mg/kg days 1–5, 10, 17, 24, 31, 38)	Other amphotericin B lipid complex dosed as for liposomal amphotericin B Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily (total dose of 1.5–2.0 g) SSG 20 mg Sb5+/kg IV/IM daily for 28 days Miltefosine 100 mg PO daily for 4 weeks
Food and Drug Administration [126]	Immunosuppression (HIV and non-HIV)	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV days 1–5, 10, 17, 24, 31, 38	
WHO [127]	HIV	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV daily or days 1–5, 10, 17, 24, 31, 38	
CL and MCL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Pentavalent antimonials[a] 20 mg Sb5+/kg IV/IM daily CL: 21 days MCL: 28 days	Conventional or liposomal amphotericin B, miltefosine, paromomycin, pentamidine, and fluconazole, based on species and availability
Centers for Disease Prevention and Control [128] (only for CL, not for MCL/ML)	HIV	Liposomal amphotericin B as for VL SSG 20 mg Sb5+/kg IV/IM daily for 28 days	Miltefosine PO, topical paromomycin, intralesional SSG, or local heat therapy

CL, cutaneous leishmaniasis; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; MCL, mucocutaneous leishmaniasis; PO, per os; SSG, sodium stibogluconate (pentavalent antimony); VL, visceral leishmaniasis.
[a]Stibogluconate or meglumine antimoniate.

Lancet Infect Dis, 2013

Lv em imunodeprimidos

- Tratamento
  - Efetividade:
    - Imunocompetentes: 93-97%
    - HIV+: 55-66%
    - Transplantados: 84%
  - Anfotericina B lipossomal (3mg/Kg/d)
  - Antimonial – alta toxicidade!
- Profilaxia secundária:
  - Não necessária????
  - Diminuir dose do imunossupressor???

Acta Trop, 2004; Ann Rheum Dis, 2012;
Lancet Infect Dis, 2008; Clin Microbiol Infect, 2014

Biological Activities of Lignoids from Amazon Myristicaceae Species: *Virola michelii*, *V. mollissima*, *V. pavonis* and *Iryanthera juruensis*[#]

Sabrina K. R. Morais,[a,b] Ana F. Teixeira,[a,c] Zelina E. dos S. Torres,[d,e] Sergio M. Nunomura,[e] Edite H. Yamashiro-Kanashiro,[f] José Angelo L. Lindoso[f] and Massayoshi Yoshida[,a,b]*

J. Braz. Chem. Soc., Vol. 20, No. 6, 1110-1118, 2009.

Table 2. Sensitivity of *Leishmania* sp. promastigote forms to lignoids

Lignoids	*L. amazonensis*	*L. braziliensis*	*L. chagasi*
	IC_{50} / (μg mL^{-1})		
1	45.0	98.0	184.0
2	27.0	100.0	170.0
6	> 250	> 250	> 250
7	76.0	> 250	> 250
8	100.0	> 250	> 250
9	> 250	> 250	> 250
10	148.0	150.0	> 250
11	> 250	> 250	> 250
12	> 250	> 250	> 250
13	> 250	> 250	> 250
14	239.0	230.0	> 250
15	> 250	> 250	> 250
17	> 250	> 250	> 250

Effects of nitro-heterocyclic derivatives against *Leishmania (Leishmania) infantum* promastigotes and intracellular amastigotes

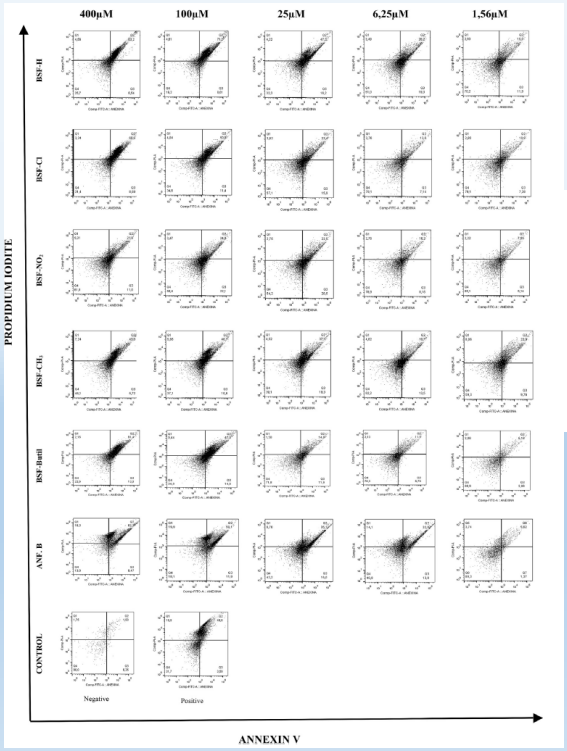
Simone Carolina Soares Petri e Silva, Fanny Palace-Berl, Leoberto Costa Tavares, Sandra Regina Castro Soares and Jose Angelo Lauletta Lindoso

Experimental Parasitology 163 (2016) 68–75

Activity of nitro heterocyclic compounds and amphotericin B against L. (L.) infantum promastigotes.

	BSF-H	BSF-CL	BSF-NO_2	BSF-CH_3	BSF-BUTIL	ANF.B
EC_{50} (μM)	0.76	0.72	0.58	2.0	1.97	0.22
95%IC	0.68 ± 0.85	0.66 ± 0.79	0.49 ± 0.68	1.8 ± 2.3	1.3 ± 2.8	0.18 ± 0.27

EC_{50}: 50% effective concentration determined after 48 h of incubation.



Evaluation of cell viability macrophages THP-1 cells without infection incubated with BSF series compounds.

	BSF-H	BSF-Cl	BSF-NO_2	BSF-CH_3	BSF-Butil	ANF. B
CC_{50} (μM)	10.5	0.06	10.9	1.9	NP	0.08
95%CI	9.02 ± 12.3	0.005 ± 3	9.2 ± 13	1.7 ± 2.16	NP	0.03 ± 2.6
IS	13.84	0.079	18.79	0.91	NP	0.36

CC_{50}: cytotoxicity concentration, CI- confidence interval, IS- index selective = IC_{50}/CC_{50}*L(L) infantum*promastigotes.

exposure by promastigotes, measured by flow cytometry, as well as nitric oxide production, measured by Griess' method. The nitro-heterocyclic compounds (BSF series) showed activity against *L. (L.) infantum* promastigotes, inducting the phosphatidylserine exposition by promastigotes, decreasing intracellular amastigotes and increasing oxide nitric production. The selectivity index was more prominent to *Leishmania* than to macrophages. Compared to amphotericin b, our compounds presented higher IC_{50},

Nanoliposomal Buparvaquone Immunomodulates *Leishmania infantum*- Infected Macrophages and Is Highly Effective in a Murine Model

Thais Alves da Costa-Silva, Andrés Jimenez Galisteo, Jr., José Angelo Lauletta Lindoso, Leandro R. S. Barbosa, Andre Gustavo Tempone

Antimicrobial Agents and Chemotherapy, April 2017 Volume 61 Issue 4 e02297-16

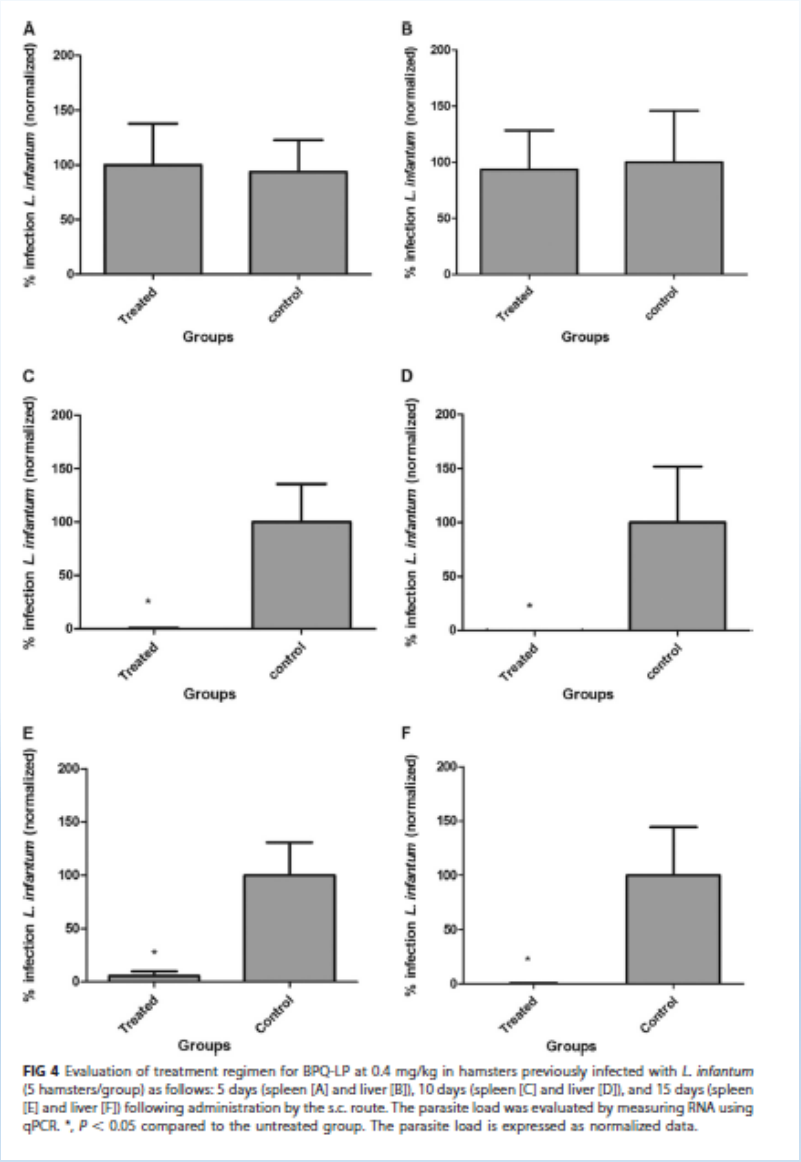


FIG 4 Evaluation of treatment regimen for BPQ-LP at 0.4 mg/kg in hamsters previously infected with *L. infantum* (5 hamsters/group) as follows: 5 days (spleen [A] and liver [B]), 10 days (spleen [C] and liver [D]), and 15 days (spleen [E] and liver [F]) following administration by the s.c. route. The parasite load was evaluated by measuring RNA using qPCR. *, $P < 0.05$ compared to the untreated group. The parasite load is expressed as normalized data.

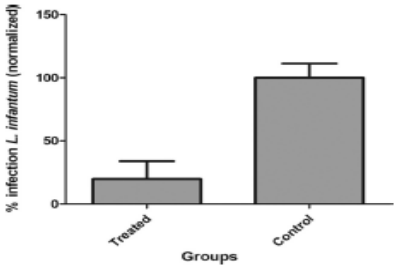


FIG 5 Evaluation of treatment regimen of BPQ-LP at 0.4 mg/kg in hamsters previously infected with *L. infantum* (5 hamsters/group) as follows: 15 days of administration by the s.c. route in the bone marrow. Data were analyzed by RT-qPCR in the bone marrow. *, $P < 0.05$ compared to the untreated group. The parasite load is expressed as normalized data.

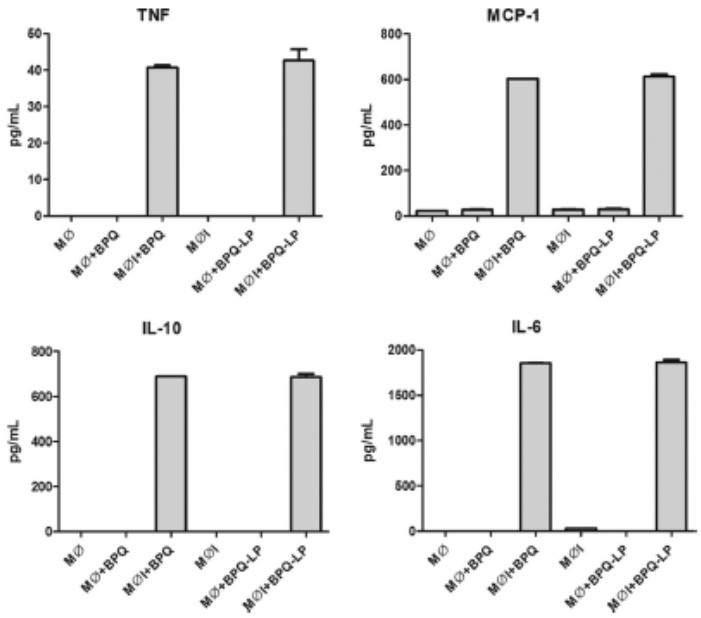


FIG 6 Effects of BPQ treatment on the production of proinflammatory cytokines (TNF, MCP-1, IL-6, and IL-10) in *L. infantum*-infected macrophages at 100 μM. The cytokines IL-12p70 and IFN-γ could not be detected. Mϕ, macrophages; MϕI, *Leishmania*-infected macrophages; Mϕ+BPQ, macrophages treated with buparvaquone; MϕI+BPQ, *Leishmania*-infected macrophages treated with buparvaquone; Mϕ+BPQ-LP, macrophages treated with liposomal buparvaquone; MϕI+BPQ-LP, *Leishmania*-infected macrophages treated with liposomal buparvaquone. The results are expressed in pg/ml, and cytokines were measured by CBA assay.

Conclusões

- Fatores de Risco
  - Risco de adoecimento
  - Risco de morte
- Manifestações clínicas
  - Dependente da resposta imune
  - Hepatoesplenomegalia: forma clássica
  - Diversidade clínica
- Terapêutica
  - Poucas drogas disponíveis
  - Imunossuprimido: qual o melhor esquema terapêutico e melhor dose ???
  - Profilaxia secundária