

Weer leishmania, en wat nu.....?

SKML

19 maart 2015

Monique Keuter & Foekje Stelma

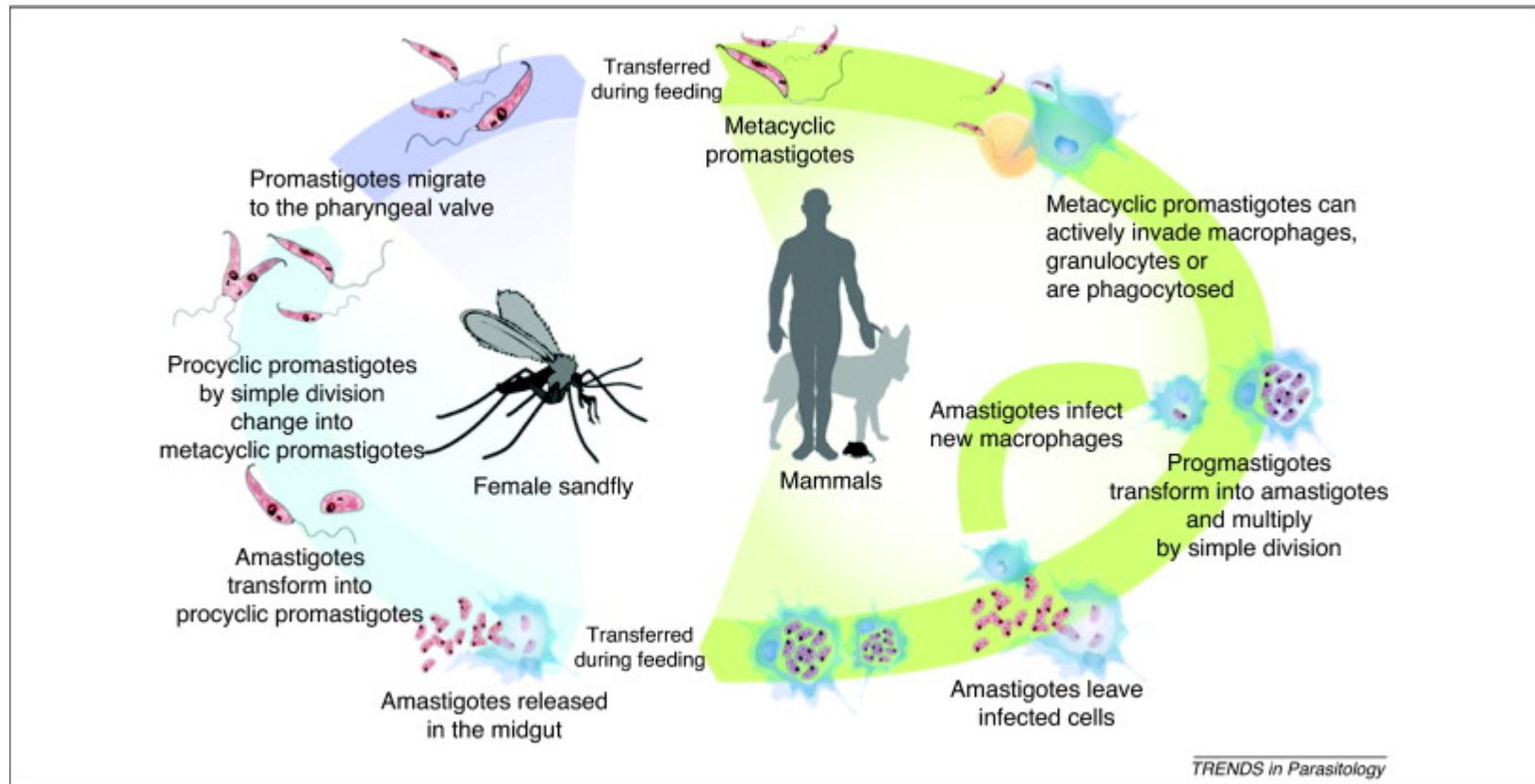


Neutrophil leishmania fagocytosis

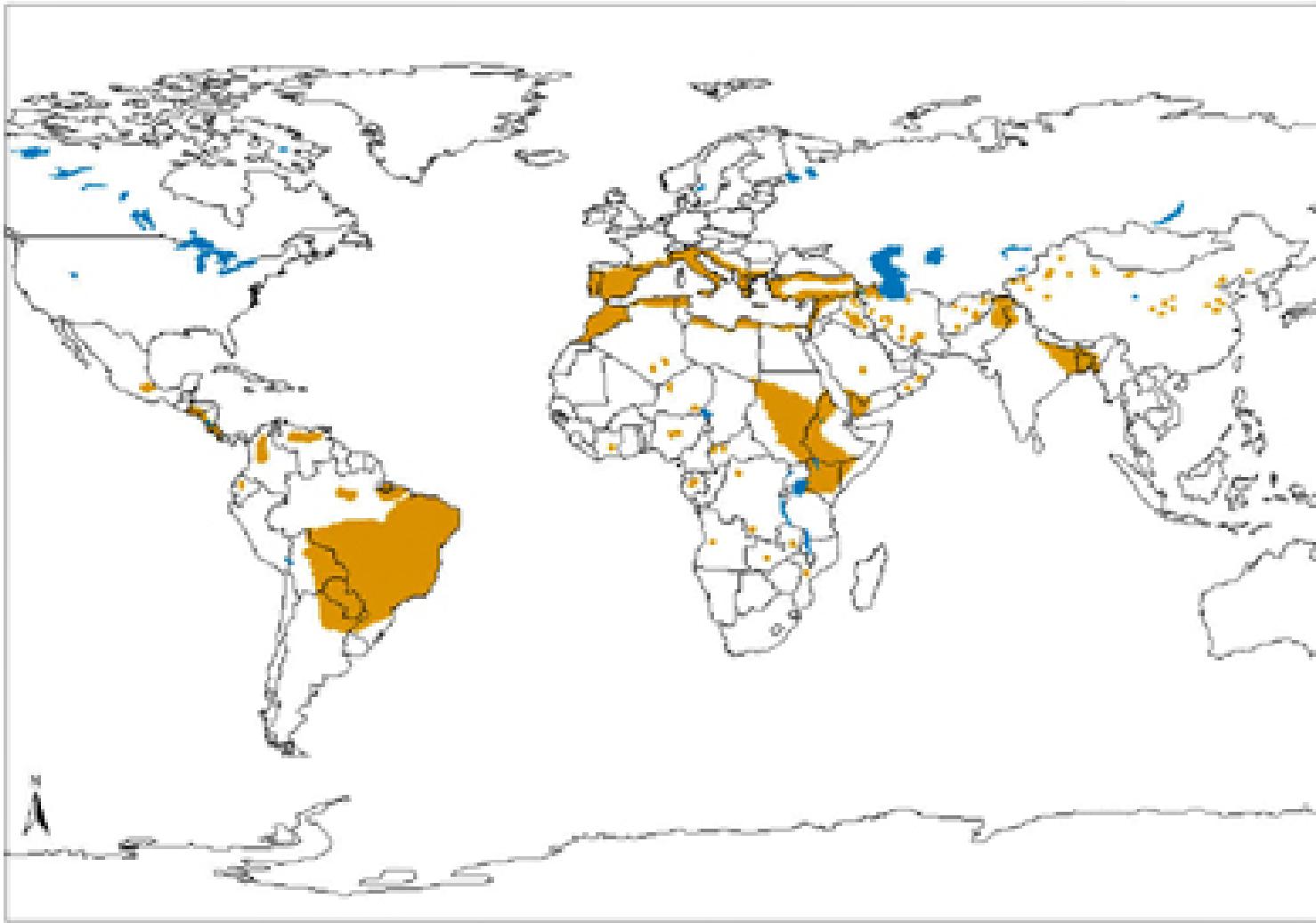
Introductie

- Leishmania is een protozoaire infectie
- Verschillende ziektebeelden
 - Cutane Leishmania (CL)
 - Mucocutane Leishmania (MCL)
 - Viscerale Leishmania (VL)
- Incidentie 2milj/jr → 25% VL
- Immun gecompromiteerde gastheer
 - latente infecties die kunnen reactiveren





Visceral leishmaniasis



75-year old male patient

Past medical history:

- 2003: kidney transplant
- July-2005: visceral Leishmaniasis (*L. infantum*) (L-amfo-B 10 days, followed by weekly gifts of 200mg for 3 months)
- Nov- 2006: relapse of visceral leishmaniasis (L-amfo-B until Jan-2007)

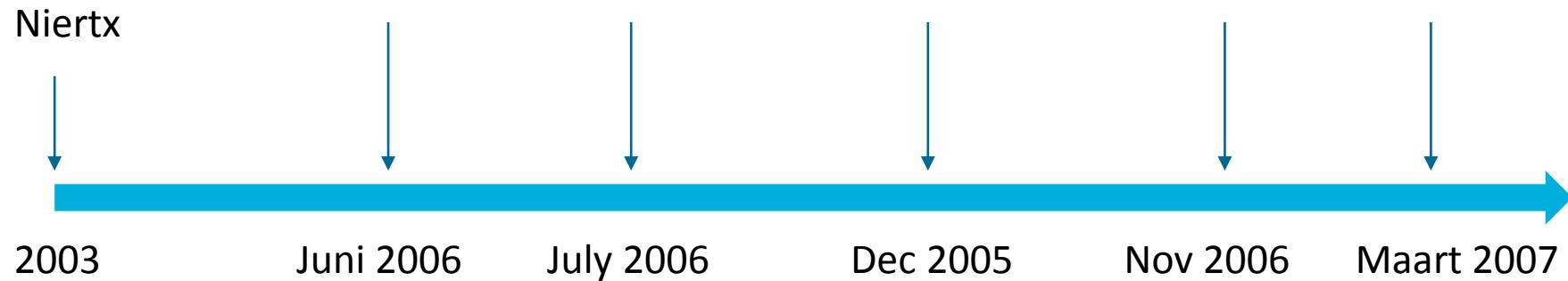
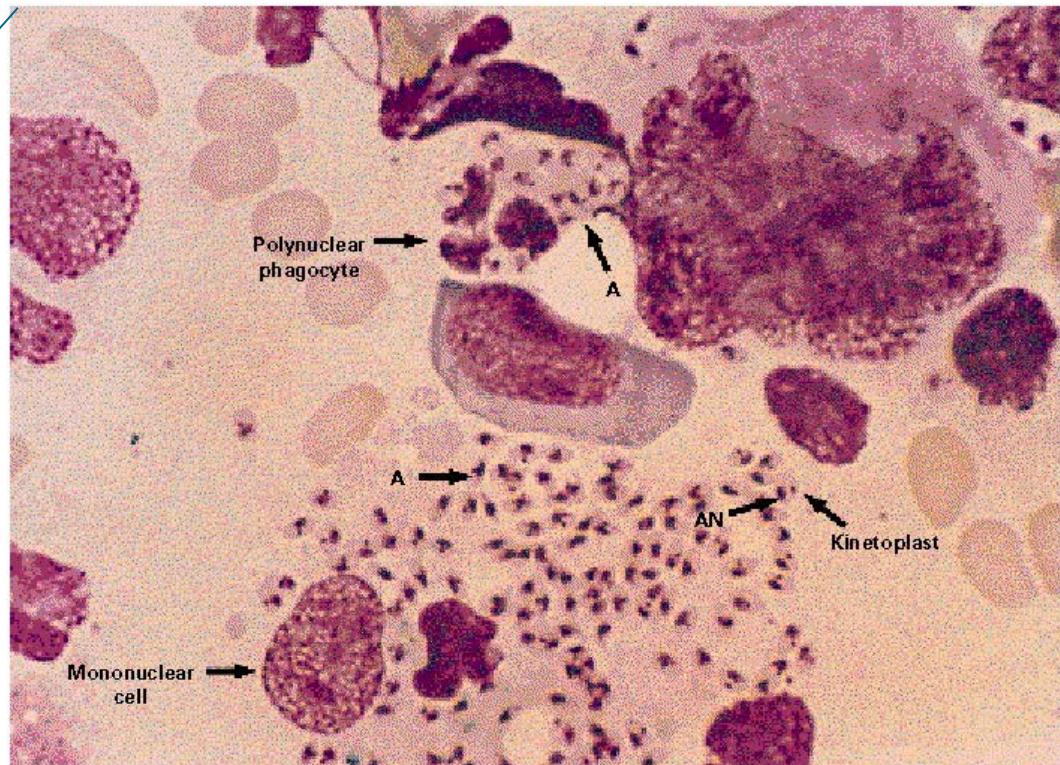
Current immunosuppressive drugs:

- Prednisolone 10mg OD
- Tacrolimus

Other: acenocoumarol, atorvastatine, esomeprazole, finasteride, ezetimib, gliclazide, insulatard, clonazepam

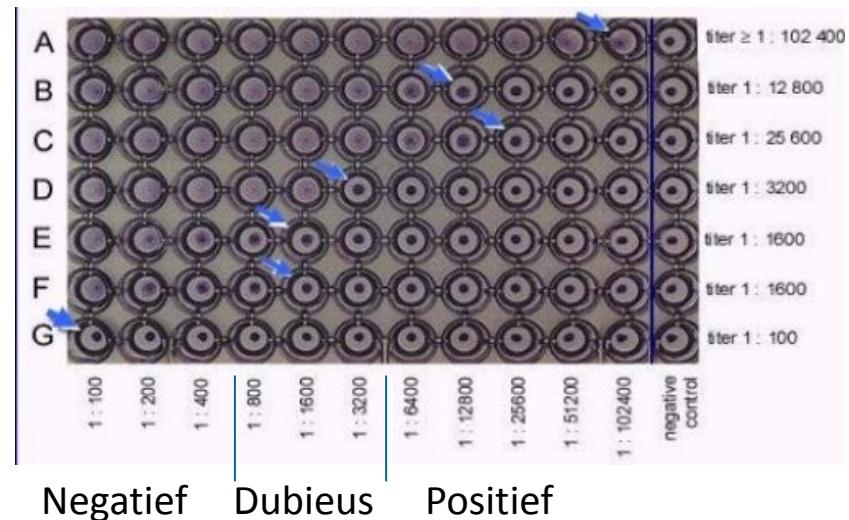
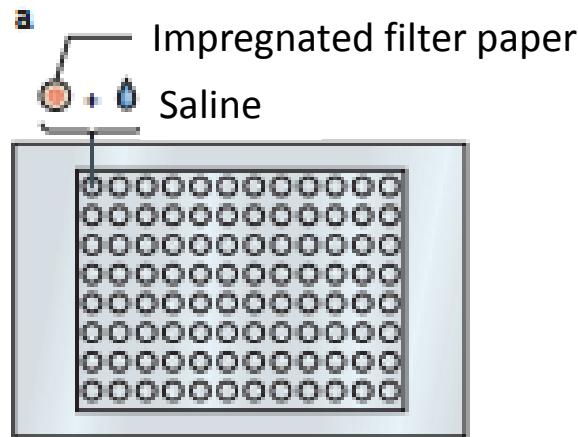
Diagnostiek Dh

PCR / typering		<i>L. infantum</i>
Kweek		Pos
Beenmerg	Neg	Pos
Leish serologie	Neg	Neg



DAT (direct agglutination test)

- Anti-leishmania antilichaam tegen gevriesdroogd antigen
 - Sensitiviteit 95%, Specificiteit 85% in HIV negatieve patienten¹
 - Sensitiviteit daalt tot 50% in HIV positieve patienten²
 - Serologie meet de blootstelling en niet actieve infectie



1) Sundar & Rai. *Clin. Diagn. Lab. Immunol.*, Sept. 2002, p. 951-958

2) Pasquau et al. Eur J Clin Microbiol Infect Dis (2005) 24: 411–418

Current complaints

- Weight loss (11kg in 4 years), fatigue, no fever, no night sweats
 - Swelling left forearm and hand.
 - No pulmonary or abdominal complaints
 - Camping in southern France before TX.
 - Last visit to Southern Europe (Spain) in 2005 (the only visit after TX)
 - Complaints led to admission 2014 November
-

Physical examination

Weak, cachectic patient. Body temperature 36.8°C.

Abdominal examination: enlarged liver, spleen not palpable.

Left forearm and hand are swollen with some skin interruptions but no ulcera.



Additional investigation

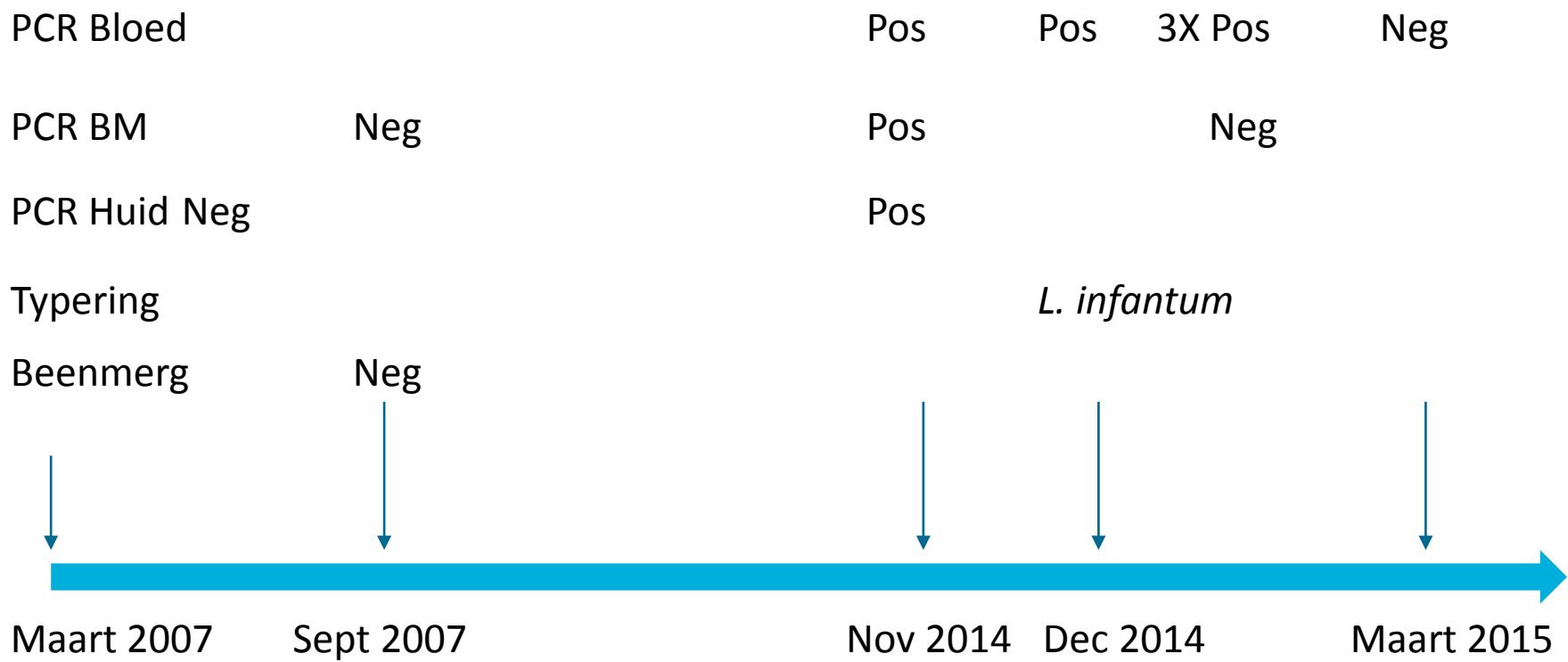
PCR Leishmaniasis (blood): positive

PCR Leishmaniasis (skin biopsy): positive

Abdominal ultrasound: spleen 15cm, hepatomegaly

Hemoglobin 6,7 Leucocytes 2,4, Trombocytes 106, CRP 42

Diagnostiek Dhr S (2)



PCR

- Target 16S rRNA¹ → 27 subspecies
- probe LEIS.P1 (5- CGGTCGGTGTGGCGCC-3)
- primers are LEIS.U1 (5- AAGTGCTTCCCATCGCAACT-3)
LEIS.L1 (5-GACGCACTAAACCCCTCCAA-3). A

Consensus Sequence:	1	34	35	67
<i>L. aethiopica</i> (M81428):	ACAAGTGCTTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. chagasi</i> (M81430):	ACAAGTGCTTCCCATCGCAAC <u>CTCGGTTCCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. donovani</i> (M80295):	ACAAGTGCTTCCCATCGCAAC <u>CTCGGTTCCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. donovani</i> (M81429):	ACAAGTGCTTCCCATCGCAAC <u>CTCGGTTCCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. donovani</i> (X07773):	ACAAGTGCTTCCCATCGCAAC <u>CTCGGTTCCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. guyanensis</i> (X53913):	ACAAGTGCTTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	
<i>L. mexicana</i> (M80293):	ACAAGCGCTCTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	
<i>L. major</i> (M81427):	ACAAGTGCTTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. mexicana</i> (M81422):	ACAAGTGCTTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	
<i>L. tropica</i> (M80294):	ACAAGTGCTTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTG--AGGGGTTAGTGCCTCCGG	
<i>L. V. complex</i> (M80292):	ACAAGCGCTCTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	
<i>L. V. complex</i> (M81416):	ACAAGCGCTCTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	
<i>L. V. complex</i> (M81421):	ACAAGCGCTCTCCCATCGCAACT <u>TCGGTTCGGTG</u>		TGTGGCGCCTTTGGAGGGGTTAGTGCCTCCGG	

FIGURE 1. Alignment of published *Leishmania* small-subunit ribosomal RNA gene sequences. Probe (LEIS.P1) and flanking S.U1 and LEIS.L1 are underlined.

Leishmania and immunesuppressive disease

Post renal tx 77% of cases (VL 86%)

Time to occurrence 6–19 mo after renal tx

Medical condition	Immunosuppressive drugs	Reference
Transplantation		
Bone marrow/ haematopoietic stem cells	Various, including steroids, cyclosporine, azathioprine, tacrolimus, and mycophenolate mofetil	[37–40,183]
Solid organ: mainly kidney; more rarely liver, heart, lung, and kidney–pancreas		[27–36,184]
Rheumatological/connective tissue diseases/vasculitis		
Rheumatoid arthritis	Various, including steroids, methotrexate, cyclophosphamide, anti-TNF- α agents	[44,46,47,51,98, 99,185–189]
Systemic lupus erythematosus		[43,45,99]
Wegener's granulomatosis		[48]
Idiopathic juvenile arthritis		[80,190]
Ankylosing spondylitis		[149,190]
Giant cell arthritis		[149]
Psoriatic arthritis		[51, 111, 191]
Other chronic inflammatory or iatrogenic immunosuppressive conditions		
Asthma	Steroids	[56]
Asthma/dermatitis	Steroids	[168]
COPD	Steroids	[58]
Cheilitis granulomatosa	Steroids	[56]
Ulcerative colitis	Azathioprine/cyclosporine	[59]
Sarcoidosis	Steroids	[57]
Myasthenia gravis	Steroids	[56]
Oncology		[61]
Haematological malignancies	Various (chemotherapy)	[60,192–195]
Solid tumours		[61]

COPD, chronic obstructive pulmonary disease; TNF- α , tumour necrosis factor- α .

^aNon-exhaustive, with priority given to more recent or particularly interesting cases.

Immunology in VL

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Review

Immune Regulation during Chronic Visceral Leishmaniasis

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Radboudumc

Asymptomatic infection

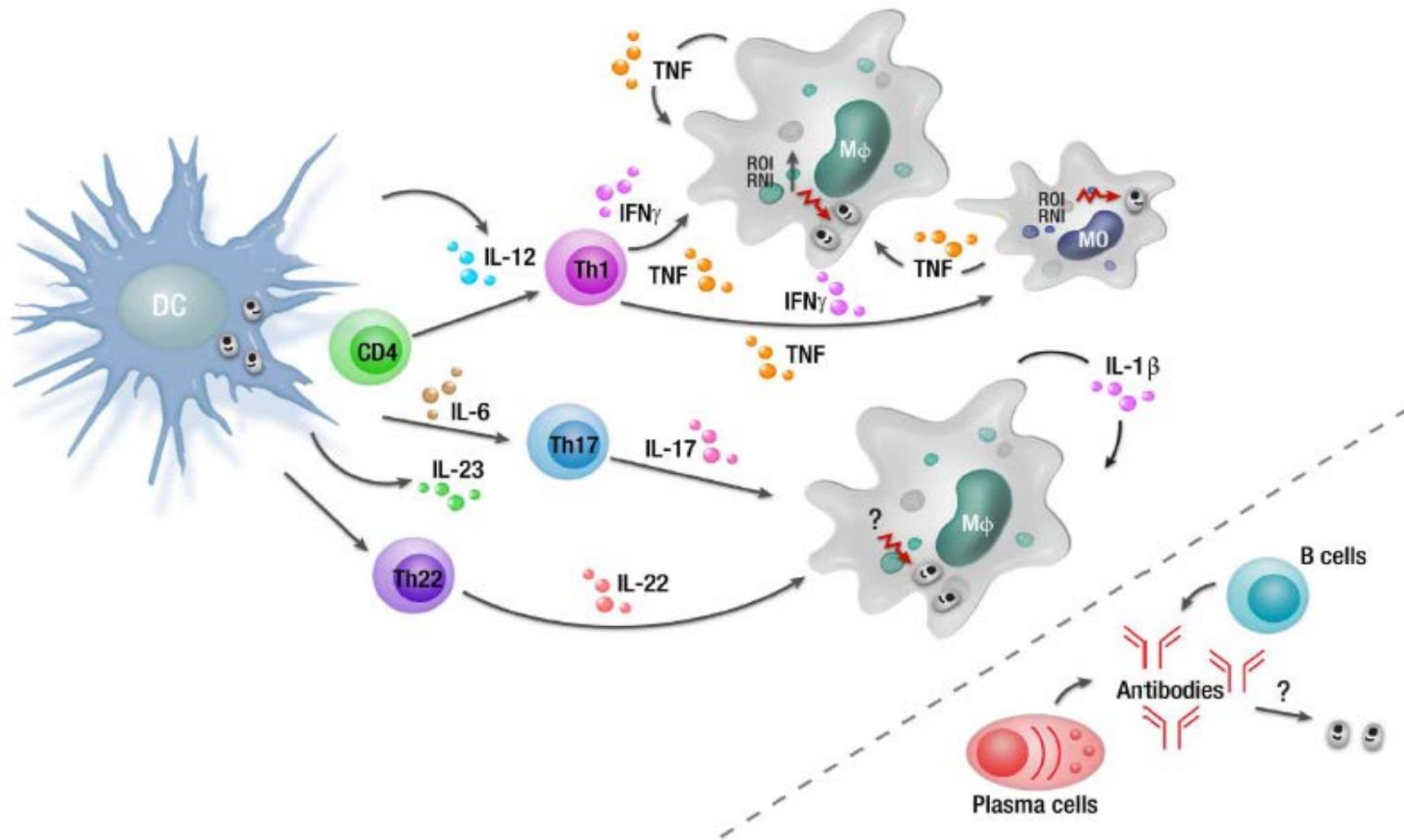
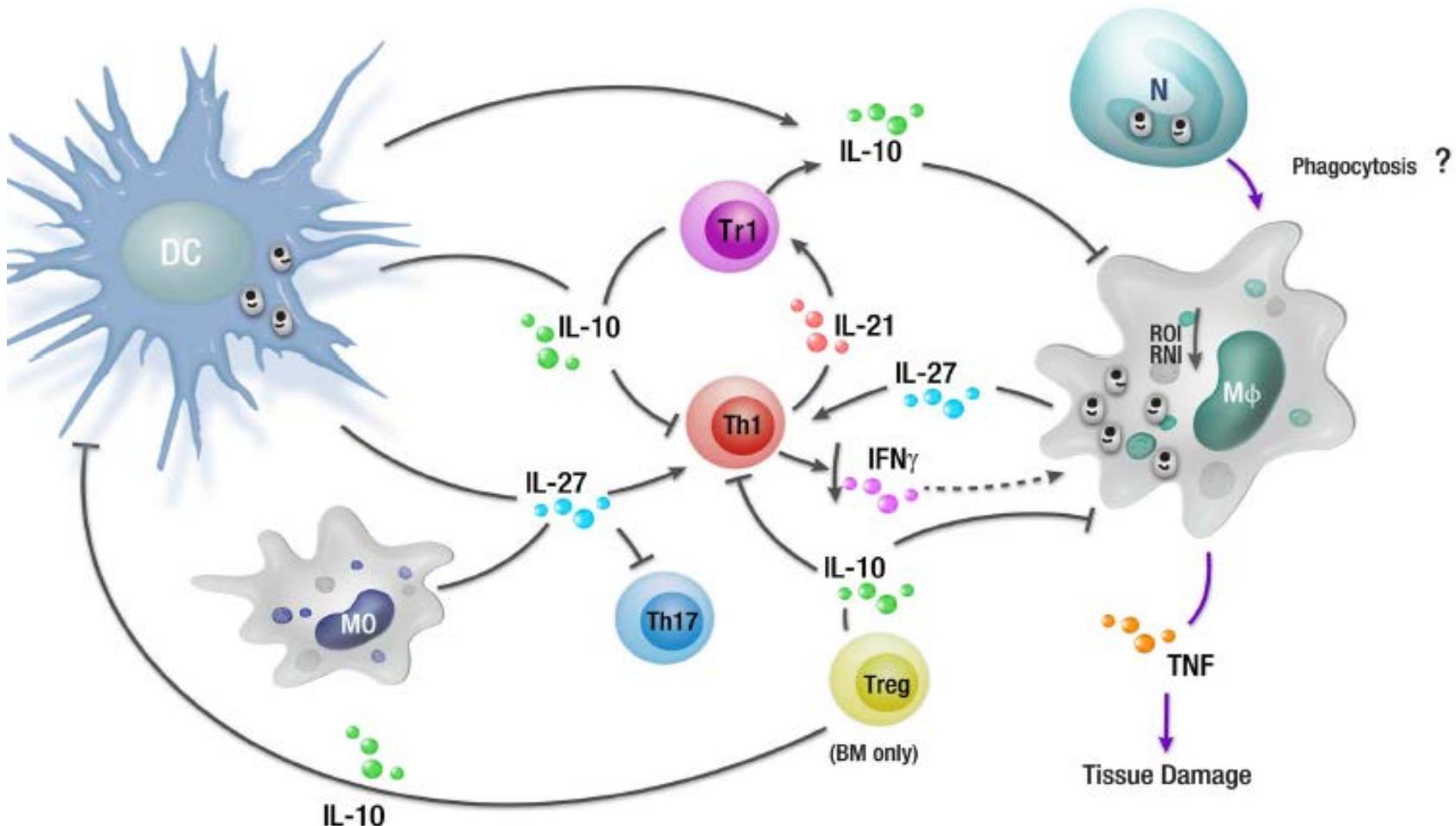


Figure 1. Overview of cellular responses during an asymptomatic *L. donovani* infection. Infected macrophages can produce TNF and IL-1 β in response to *L. donovani* infection as part of the innate immune response. However, DC IL-12 production in response to *L. donovani* infection is

Chronic infection (spleen)



Treatment

Visceral leishmaniasis

- Pentavalent antimonials
- Amphotericin B
- Miltefosine
- Paromomycin

Cutaneous leishmaniasis

- Pentavalent antimonials
- Pentamidine
- Paromomycin

Mucosal leishmaniasis

- Pentavalent antimonials

Leishmania treatment

Organization	Target group	Preferred therapy	Alternative therapy
VL			
American Society of Transplantation and American Society of Transplant Surgeons [141] Centers for Disease Prevention and Control [128]	Organ transplant HIV	Liposomal amphotericin B 21 mg/kg total dose 3 mg/kg IV days 1–5, 14, 21 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)	Amphotericin B deoxycholate 1.0 mg/kg daily for 15–20 days or a pentavalent antimony compound ^a 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] Centers for Disease Prevention and Control [128] (only for CL, not for MCL/ML)	Organ transplant HIV	Pentavalent antimonials ^a 20 mg Sb5+/kg IV/IM daily CL: 21 days MCL: 28 days Liposomal amphotericin B as for VL SSG 20 mg Sb5+/kg IV/IM daily for 28 days	Conventional or liposomal amphotericin B, miltefosine, paromomycin, pentamidine, and fluconazole, based on species and availability 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.

^aStibogluconate or meglumine antimoniate.

Start treatment Nov 2014

Liposomal Amphotericin B

3mg/kg/day

Tacrolimus was changed to MMF

Because of leukopenia MMF was decreased in dose

Because of S aureus super infection arm flucloxacillin was given

$70 \times 40 \text{ mg/kg L-AmB} = 3 \text{ grams}$

Parameter of success? Leukopenia, clinical symptoms, Leish PCR?

Diagnostics

Radboudumc

species and clinical syndromes

Species	Distribution	Disease
<i>L. donovani</i>	Africa, India, Mediterranean	Visceral Leishmaniasis
<i>L. infantum</i>		
<i>L. chagasi</i>	South America	
<i>L. mayor</i>	Africa, India, Mediterranean	Cutaneous Leishmaniasis
<i>L. tropica</i>		
<i>L. aethiopica</i>		
<i>L. mexicana</i>	South and Central America	
<i>L. braziliensis</i>		
<i>L. peruviana</i>		

52 episodes 19 patients

Case report

Recurrent leishmaniasis in kidney transplant recipients: report of 2 cases and systematic review of the literature

2011 Transplant Infectious Disease; 13: 397-406

Treatment in 52 episodes

Relapses 1 m to 5 yrs after initial diseases

Median Follow up mostly < 18 months (4 died)

- 2/3 pentavalent antimonials

2 severe side effects on antimonials (pancreatitis)

Thereafter L-AmB

- 1/3 L-AmB total dose not more than 2,5 gram (costs !?)
- 1x paromomycin iv (dose unknown)
- 1x miltefosine 28 days (pt died)

Prophylactic drugs not used except in 2 patients

L-AmB 150 mg/3 weeks and 1x antimonials

Consensus treatment ?

The authors think that the L-AmB dose to use for possible prophylaxis should be not less than 3mg/kg monthly.

Miltefosine could become an interesting alternative for secondary prophylaxis in the future.

Prophylactic drugs should be continued while highly Immunosuppressive drugs are administrated

Conclusion patient S

M. 75 yr kidney transplant,
Recurrent visceral leishmaniasis
L-AmB Ambisome IV > 9 grams

09-03: PCR leishmaniasis neg.
Neutropenia BM Leishmaniasis
and MMF



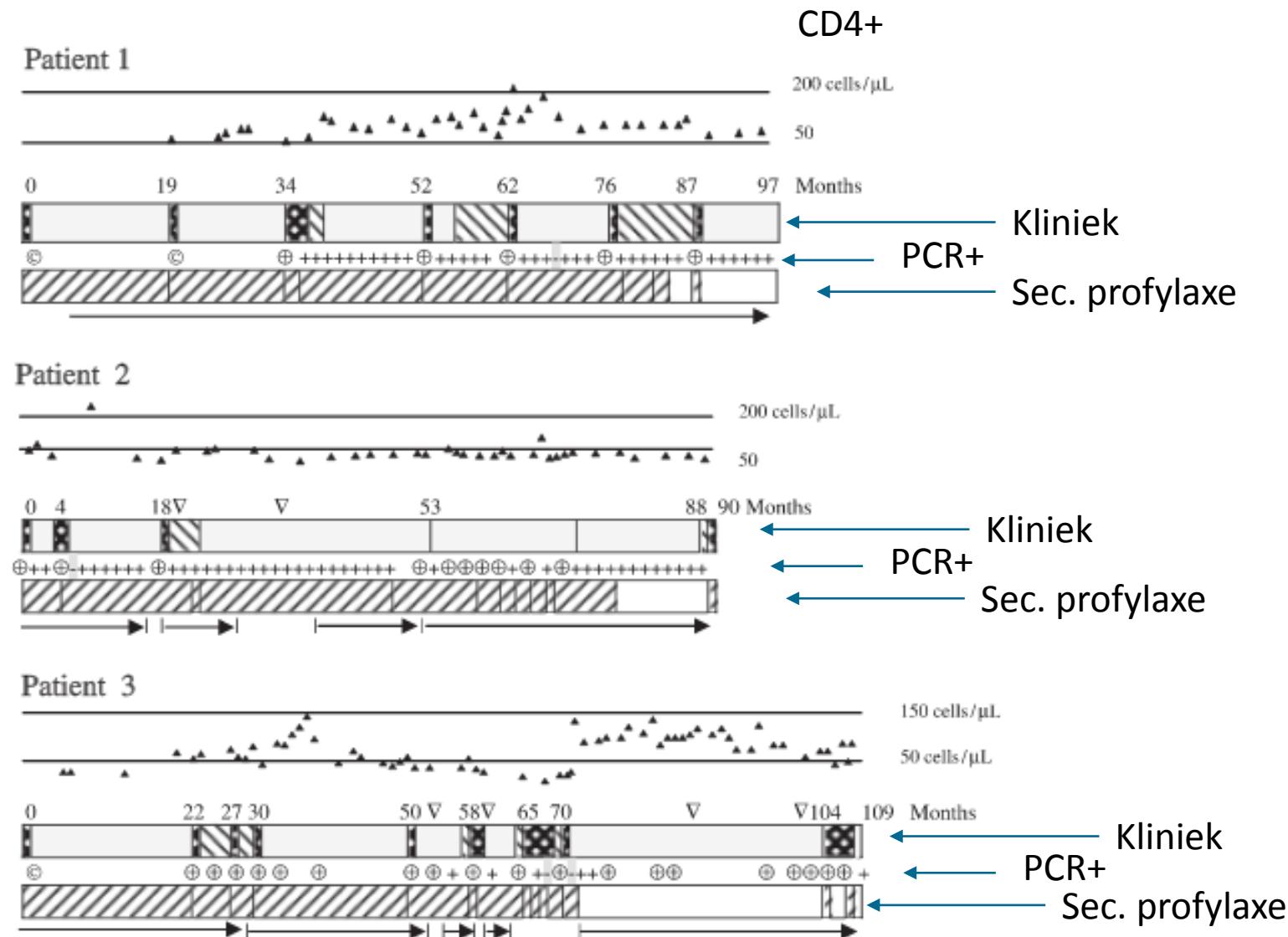
Plan: at least monthly L-AmB iv

How to follow up PCR??

Technique	Tissue/fluid	Immunosuppression	Sensitivity (%)	Invasiveness	Feasibility (field use)	Reference
Microscopy	Blood	HIV	50	+	+	[18]
	Spleen	HIV	>95	+++	+	[18]
	Bone marrow	HIV	67–94	++	+	[18]
	Lymph node	HIV	53–65	++	+	[196]
	Bone marrow	SOT	98	++	+	[31]
Culture	Bone marrow	Other	100	++	+	[85]
	Bone marrow	HIV	70–81.3	++	+	[31,197]
		SOT	82.0	++	+	[31]
IFAT	Blood	HIV	67	+	+	[113]
	Serum	HIV	48–75	+	+	[117,197]
		SOT	92	+	+	[31]
DAT PCR	Serum	Other	100	+	+	[85]
	Blood	HIV	87.80	+	++	[198]
	Bone marrow	HIV	72–100	+	+	[121,122, 199,200]
Detecting and monitoring after treatment						
Latex agglutination test	Urine	HIV	82–100	++	+	[121,122, 199,200]
rK39 dipstick	Serum	HIV	48–85.7	–	++	[124,201]
			46.6–93.9	+	++	[198,202]

DAT, direct agglutination test; HIV, human immunodeficiency virus; IFAT, indirect fluorescent antibody test; SOT, solid organ transplant.

HIV / Leishmania co-infectie → voortdurende ziekte activiteit



Predictoren voor reactivatie VL bij HIV

Gunstige prognose indien

- CD4 > 100 bij diagnose Leishmania
- Toename CD4 tijdens behandeling leishmania
- Secundaire profylaxe

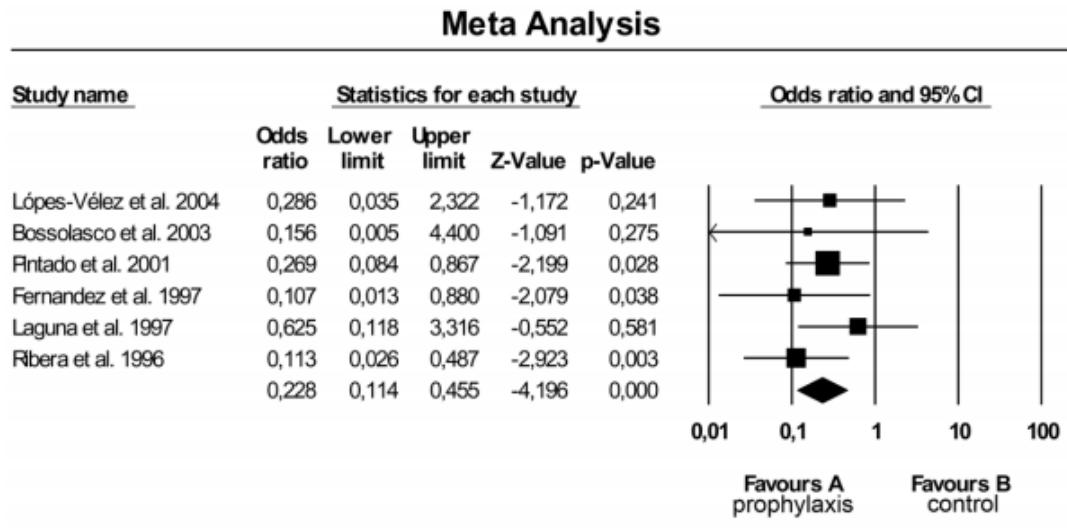


Figure 3. Meta-analysis of secondary prophylaxis results. Footnote: $I^2 = 0\%$ Egger test for publication bias was negative, $p = 0.76$.
doi:10.1371/journal.pntd.0001153.g003

Moleculaire parasitemie correleert met kliniek

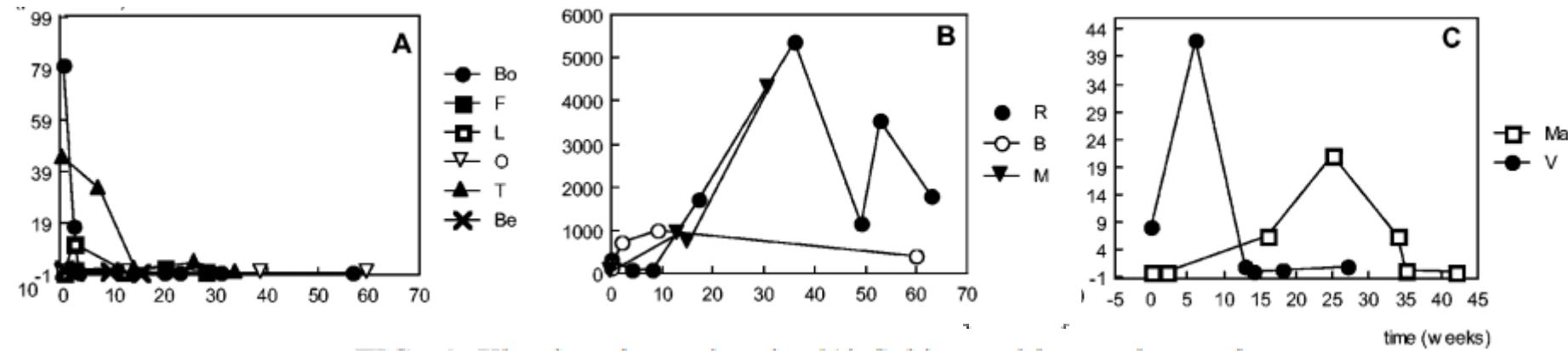


FIG. 6. Kinetics of parasitemia. (A) Subjects without relapse after Ambisome therapy. (B) Patients who do not control parasite development. R was a coinfecting patient who refused any antileishmanial treatment, B was a coinfecting patient resistant to treatment, and M was an older subject resistant to meglumine and Ambisome treatment. (C) Typical relapses in coinfecting patients; peaks of parasitemia coincide with clinical symptoms.¹

Kwantitatieve PCR wordt in de literatuur aangeraden voor diagnose en follow-up na behandeling van VL bij transplantatiepatienten².

1) Mary et al., *J. Clin. Microbiol.*, Nov. 2004, p. 5249–5255

2) Bouchehoua et al., *Transplantation Reviews* 28 (2014) 32–35

Vrouw V 60 jaar

- sept 2012 Italie, veel gebeten, huidallergie, 3 wk geduurde
- okt 2012 bleven twee huidafwijkingen over
- Tevens moe moe moe
- VL onderzoek bloedbeeld en echo buik
- huidbiopt
- Reisanamnese verder :
- 2006: Australië
- 2006: Zuid Afrika
- daarvoor elk jaar Australië, ook ZO Azie (vanaf 1988 - 2000), Maleisië, Borneo.





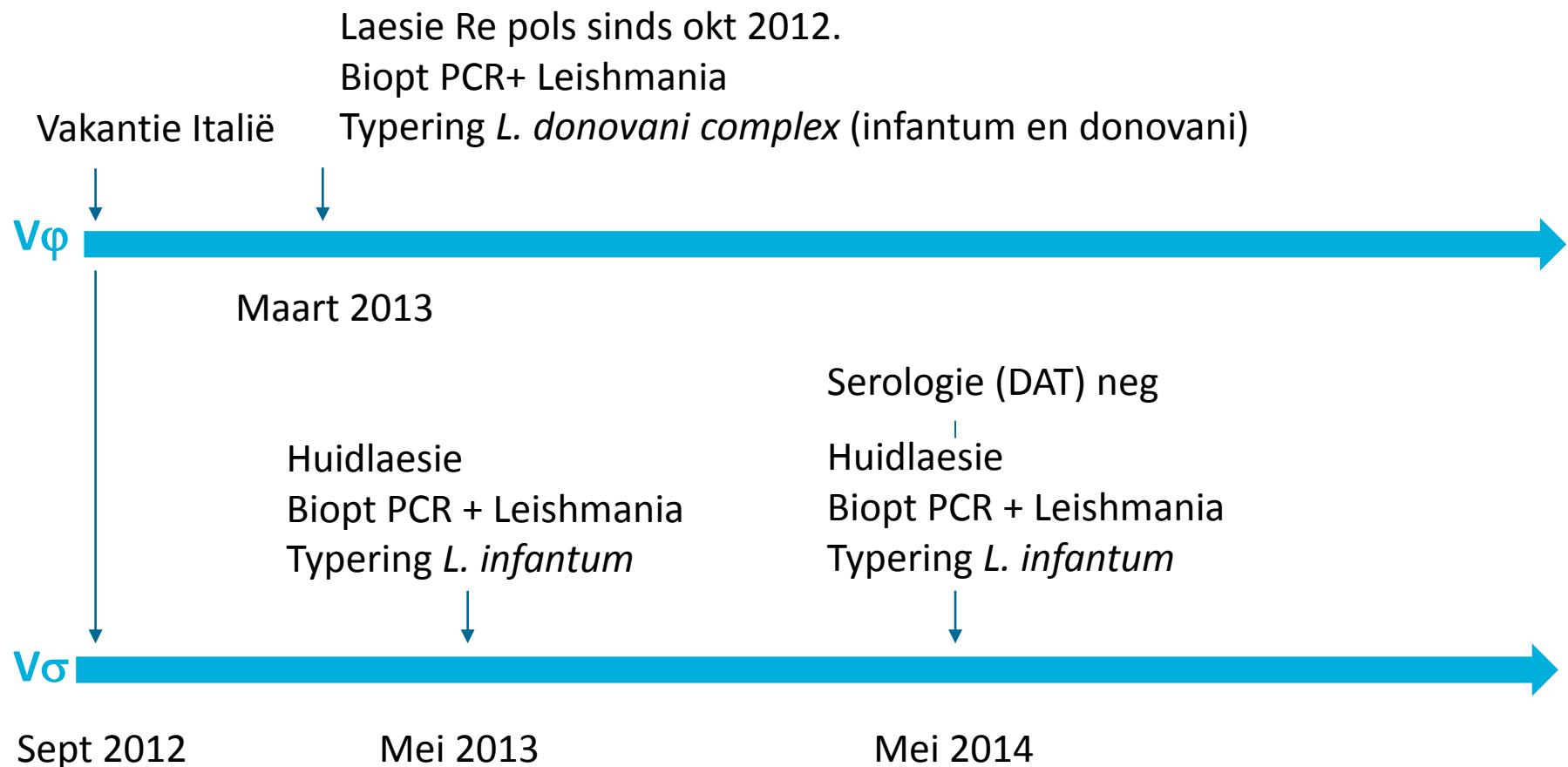
Man pt V 68 jaar

- sept 2012 Italie, veel gebeten,
- nov 2012 bleven twee huidafwijkingen over
- Reisanamnese verder :
- 2006: Australië
- 2006: Zuid Afrika
- daarvoor elk jaar Australië, ook ZO Azie (vanaf 1988 - 2000), Maleisië, Borneo.





Diagnostiek echtpaar V (Vφ en Vσ)



Echtpaar V 60 en 68 jaar

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Species-Directed Therapy for Leishmaniasis in Returning Travellers: A Comprehensive Guide

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REVIEW

LeishMan Recommendations for Treatment of Cutaneous and Mucosal Leishmaniasis in Travelers, 2014

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MD,|||| Gloria Morizot, MD,§ Christoph Hatz, MD,*†‡ Thomas P.C. Dorlo,¶¶ and
Diana N.J. Lockwood, MD##



In totaal 4x
Intralesionaal
pentostam
Zeer pijnlijk
Lidocaine bij

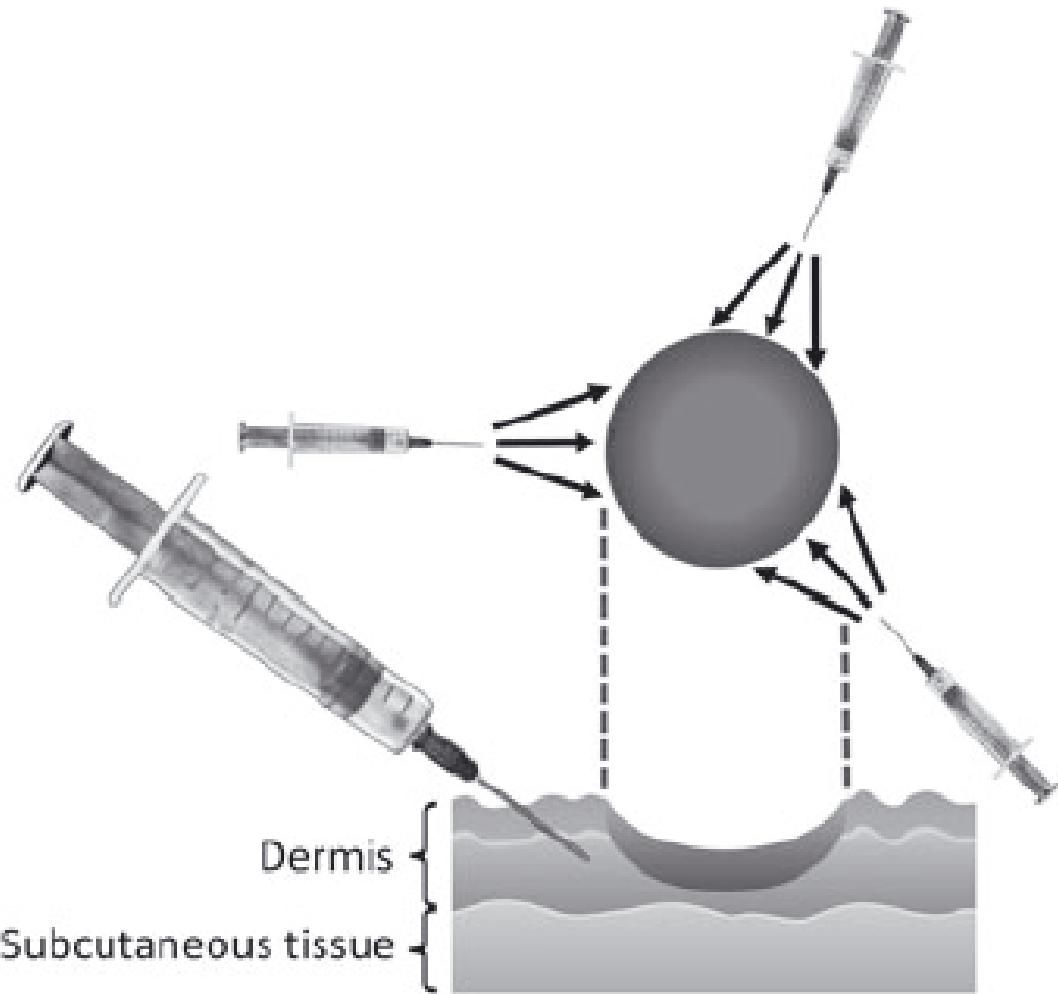


Figure 1 Procedure for intralesional treatment with pentavalent antimony.⁴⁶ Advance the needle while injecting under pressure in the dermis, covering the whole lesion including the center.

LEISHMANIASIS bij Nederlanders na vakantie zuid Europa

