Conflict of Interest

The author has declared no conflict of interest.

A randomised, open label trial to determine the efficacy and safety of combining *thermotherapy and miltefosine* for the treatment of *cutaneous leishmaniasis* in the New World

Byron Arana

Drugs for Neglected Diseases *Initiative* (DND*i*)

Geneva, Switzerland

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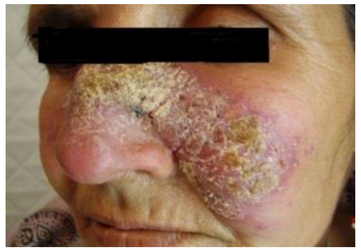
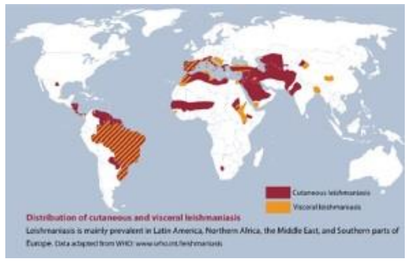
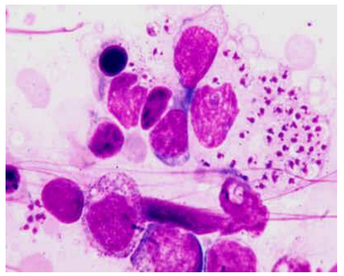
SCIENTIFIC DAYS

Global burden of cutaneous leishmaniasis (CL)



Courtesy from A. Llanos-Cuentas





- 0.7 – 1.2 million new CL cases annually worldwide
- A new case of CL every 30 seconds
- Leishmaniasis is endemic in 87 countries (2016)*
- 12 countries represented 90% of the global burden of CL cases in 2018*

- Clinical and epidemiological diversity
- No vaccine
- No chemoprophylaxis
- Limited number of drugs with variable efficacy

*WHO Weekly Epidemiological Bulletin N0 40, 5 October 2018

CL is a particularly neglected disease

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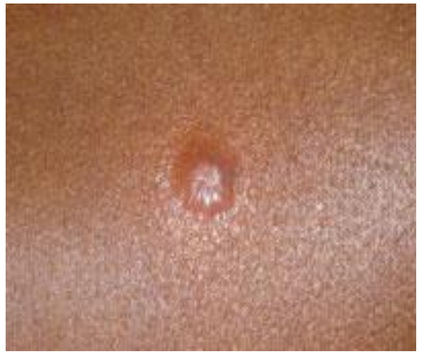
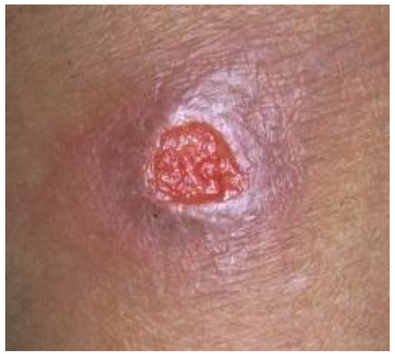
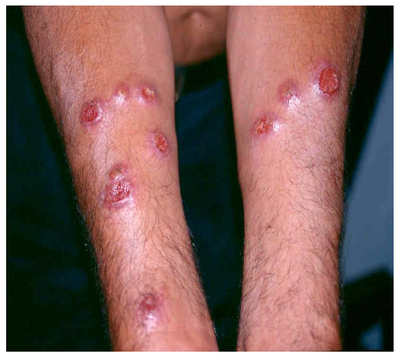
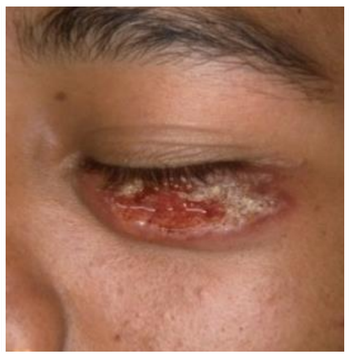
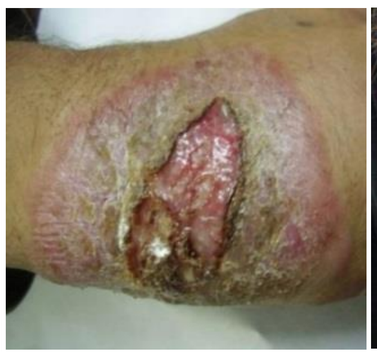
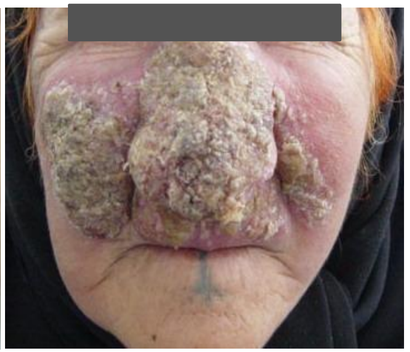
SCIENTIFIC DAYS

Current treatment recommendations for CL

Disease severity

No treatment	Topical	Systemic	Combinations
Small lesions *Leishmania major* or *L. mexicana* not in face/joints	≤ Four lesions ≤ 4 cm diameter not in face/joint • thermotherapy • liquid nitrogen • intralesional sodium stibogluconate • paromomycin cream	Topical treatment unsuccessful > Four lesions or lesions > 4 cm diameter any anatomical location • antimonials • miltefosine • pentamidine • amphotericin B deoxycholate • AmBisome® • fluconazole	• antimonials + liquid nitrogen • antimonials + allopurinol for *L. recidivans* • antimonials + paromomycin for *L. aethiopica* • antimonials + pentoxifylline for mucocutaneous leishmaniasis

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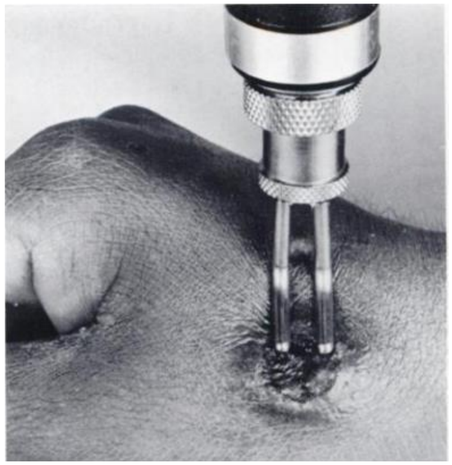
SCIENTIFIC DAYS

Potential thermotherapy + miltefosine combination treatment

Thermotherapy (TT)

- ThermoMed™ device
- Produces heat utilising radio-frequency technology
- It is the most tested local heat modality
- Safety and efficacy demonstrated in multiple randomised clinical trials
- WHO- and FDA-approved treatment for CL and other skin conditions



Miltefosine (MLT)

- The only oral treatment currently available for leishmaniasis
- FDA registered for treatment of infections due to *L. braziliensis, L. guyanensis,* and *L. panamensis* in 2014
- Included in PAHO treatment guidelines and strategic fund list of medicines in 2015

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SCIENTIFIC DAYS

Study to determine the efficacy and safety of thermotherapy + miltefosine combination

Study design

Randomised, open label, multicentre, phase 2, clinical superiority trial

- 130 patients randomly allocated to receive either:
  - One session of **TT** at 50^0C for 30"
  - One session of **TT** at 50^0C for 30" **+ MLT** 2.5 mg/kg/day for 21 days

Ethical approvals from participating institutions and local health authorities from both countries were obtained. Registered in clinicaltrials.gov NCT02687971

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SCIENTIFIC DAYS

Study to determine the efficacy and safety of thermotherapy + miltefosine combination

Primary endpoint

The proportion of initial clinical cure rate for each regimen measured at day 90

Initial cure

- Ulcerated lesions: 100% re-epithelialisation of the lesion(s) on day 90
- Non-ulcerated lesions: flattening and/or no signs of induration of the lesion(s) on day 90 (a*ssessment done by blind investigators at each study site*)

Secondary endpoints

- **Final cure**: number of patients who fulfill the criteria of initial cure and have no relapse by day 180
- Frequency, severity, and seriousness of adverse events (AEs) by treatment group

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Inclusion criteria

Patients with the following characteristics:

❖≥18 and ≤60 years

❖ Confirmed parasitological diagnosis of CL

❖ Lesions that satisfy the following criteria:
- Lesion size ≥0.5 cm and ≤4 cm
- Not located on the ear, face, close to mucosal membranes, joints, or in a location where is difficult to apply TT
- ≤four lesions
- Duration of lesion <4 months

❖ Signed written informed consent

❖ Capable of understanding and complying with the protocol

Exclusion criteria

❖ Female with a positive urine pregnancy test at screening or who is breast-feeding, lactating, or at fertile age and does not agree to use contraception up to day 90

❖ Has laboratory values at screening as follow:
- Serum creatinine above normal level
- ALT / AST three times above normal range

❖ Patient who is not willing to attend the trial visits or is not able to comply with follow-up visits up to 6 months

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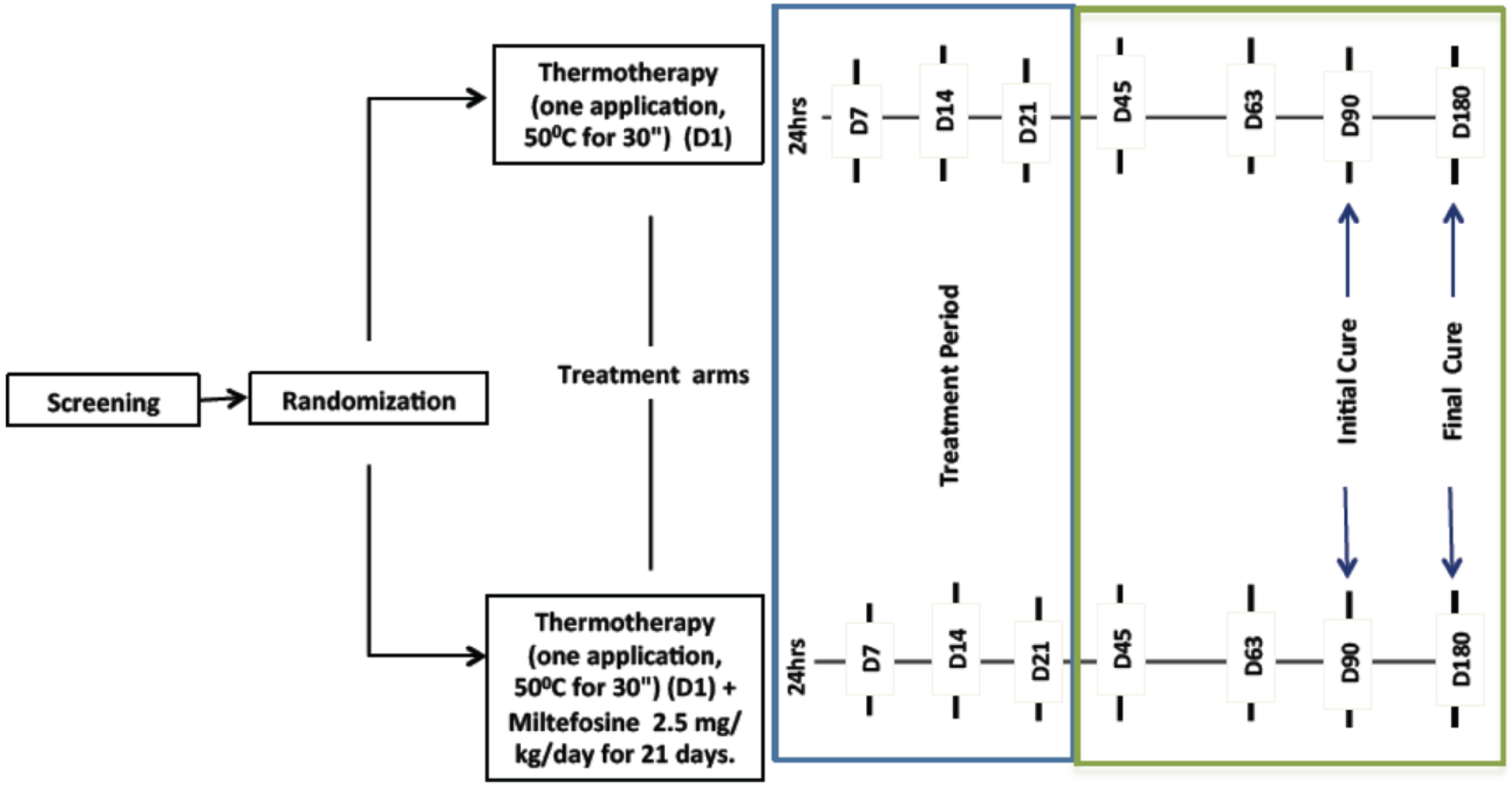
Study design



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SCIENTIFIC DAYS

Patient outcomes per treatment group

Thermotherapy patient outcomes (n=64)	
Completed the study	36
New lesions	6
Withdrew informed consent	5
Lost to follow-up	3
Failure	14*

*Late responders (day 105)= 6

Thermotherapy + miltefosine patient outcomes (n=66)	
Completed the study	52
New lesions	3
Relapse	1
Lost to follow-up	3
Failure	7*

*Late responders (day 105)= 1

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SCIENTIFIC DAYS

Patient and lesion characteristics by treatment group

Characteristics	Thermotherapy (n=64)	Thermotherapy + miltefosine (n=66)	All (n=130)
Gender			
Male (%)	48 (75.0)	52 (78.8)	100 (76.9)*
Female (%)	16 (25.0)	14 (21.2)	30 (23.1)**
Age (Years) Mean (SD)	34.3 (11.3)	35.2 (11.9)	34.8 (11.6)
Weight (Kg) Mean (SD)	71.2 (12.7)	73.1 (12.9)	72.2 (12.8)
Lesion Characteristics			
Ulcer diameter D1 (cm^2) (SD)	2.16 (2.19)	3.08 (3.2)	2.64 (2.8)
Number of lesions, mean (SD)	1.32 (0.6)	1.47 (0.8)	1.4 (0.7)
1 Lesion (%)	47 (73.4%)	45 (68.18%)	92 (70.77%)
2 Lesions (%)	14 (21.9%)	14 (21.21%)	28 (21.64%)
3 Lesions (%)	2 (3.13%)	4 (6.06%)	6 (4.62%)
4 Lesions (%)	1 (1.57%)	3 (4.55%)	4 (3.08%)
***Leishmania* specie**			
L. braziliensis (%)	8 (12.5%)	16 (24.2%)	24 (18.4%)
L. panamensis (%)	19 (29.6%)	20 (30.3%)	39 (30.3%)
L. peruviana (%)	5 (7.8%)	3 (4.5%	8 (6.1%)
L. braziliensis / L. peruviana (%)	6 (9.5%)	8 (12.3%)	14 (10.7%)
Other (%)	8(12.6%)	3 (4.5%)	11 (8.4%
No amplification (%)	15 (23.4%)	14(21.2%)	29 (22.3%)
Not done (%)	3 (4.6%)	2(3.0%)	5(3.8%)

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PAHO 2019 leishmaniasis epidemiological report of the Americas: 68.7% of all CL cases in 2017 reported in LA were male

* 70% of CL patients seen in Peru study site and 72% in Colombia study site were male

** No females were excluded from the study due to refusing the use of contraception

SCIENTIFIC DAYS

Per protocol (PP) and intention to treat (ITT) analysis

Initial and final cure by treatment groups

PP/ITT	Thermotherapy	Thermotherapy + miltefosine	P value & 95% CI
PP (day 90)	37/56 (66.1%)	53/62 (85.5%)	p= 0.011. Dif 19.4% 95% CI 2.52 – 36.28
PP (day 180)	36/56 (64.3%)	52/62 (83.9%)	p= 0.012. Dif 19.6% 95% CI 2.37 – 36.83
ITT (day 90)	37/64 (57.8%)	**53/66 (80.3%)**	p= 0.009. Dif 22.49% 95% CI 5.51 – 39.47
ITT (day 180)	36/64 (56.3%)	**52/66 (78.8%)**	p= 0.005. Dif 22.5% 95% CI 5.31 – 39.69

Six subjects in the TT arm and one in the TT+MLT arm who achieved 100% re-epithelisation of their lesions at day 105 were considered failures at day 180 of analysis

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Adverse events (AEs) reported (n)

	Thermotherapy	Thermotherapy + miltefosine
Number of AEs reported	142 in 48 subjects (75%)	234 in 56 subjects (84.8%)
Related to TT	79	74
Related to MLT	0	114
Local adverse reactions	# of subjects	# of subjects
Pain	9 (14.1%)	3 (4.5%)
Erythema	18 (28.1%)	19 (28.8%)
Local oedema	20 (31.3%)	18 (27.3%)
Vesicles	48 (75%)	55 (83.3%)
Local infection	4 (6.2%)	3 (4.5%)
Gastrointestinal disorders		
Vomiting	0	39 (59%)
Nausea	0	17 (25.7%)
Abdominal pain	0	9 (13.6%)
Diarrhoea	0	4 (6%)
AST / ALT elevation	0	20 (30.3%)

- Majority of TT's AEs (78%) were reported within the first 24 hours after TT application
- Six subjects temporally interrupted (1-2 doses each) their treatment with MLT due to nausea / vomiting
- All subjects recovered without any complications
- Three serious AEs not related to the study interventions were reported

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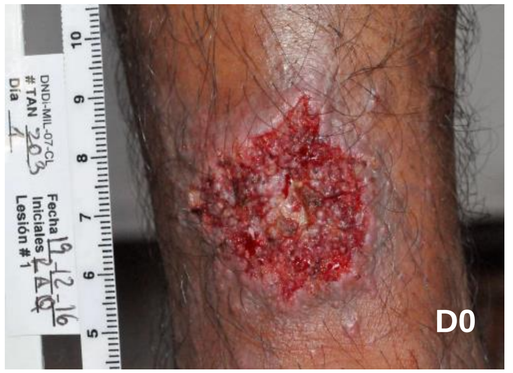
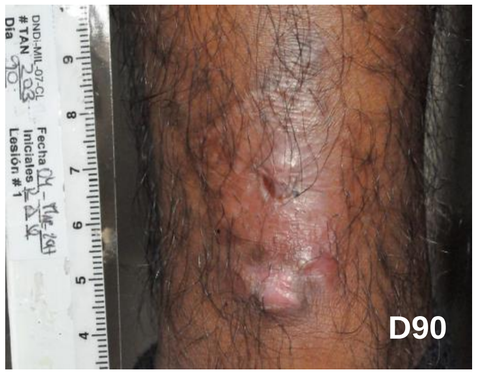
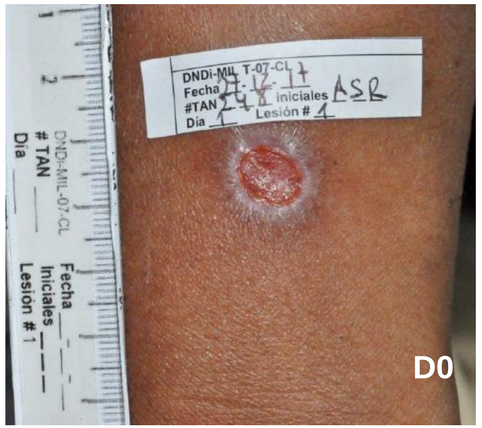
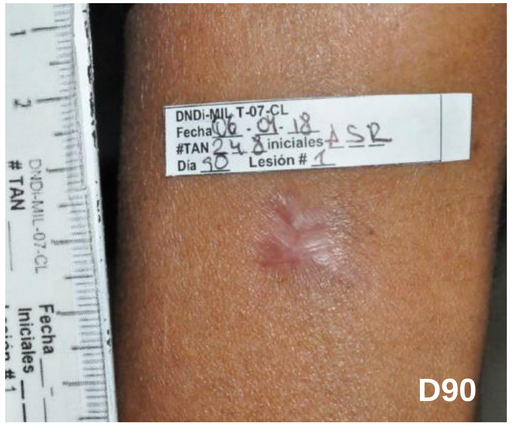
Secondary endpoints

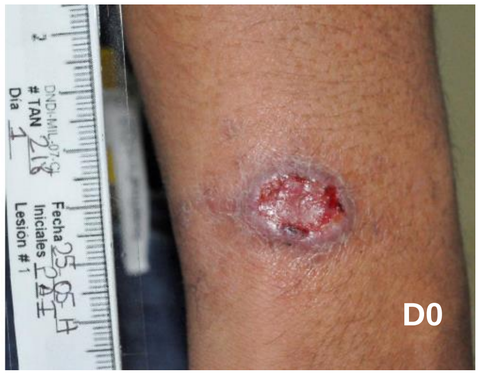
- **New lesions** in nine subjects: three (4.6%) in the TT + MLT arm and six (9.2%) in the TT arm, between day 1 and 90
- **Relapse** in one subject: TT + MLT arm, day 180
- **Lost during follow-up period:** six subjects (4.6%), three in each study arm
- Subjects with lesions due to ***L. braziliensis*** and/or ***L. peruviana*** responded better to the TT + MLT (22 [74.1%] of 27) than to TT alone (seven [36.8%] of 19)
- No differences were found in subjects with lesions due to ***L. panamensis*** (sample size was not calculated to find differences between *Leishmania* species)

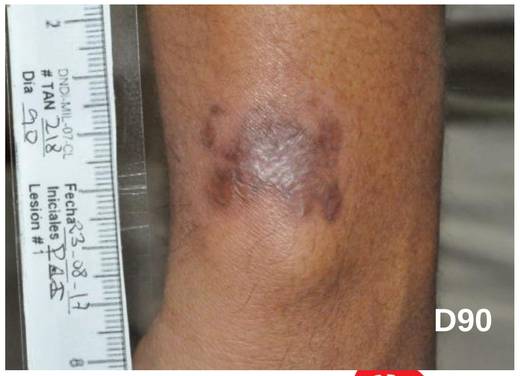












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Conclusions

- *We can improve existing tools by combining them.* The combination of **thermotherapy plus miltefosine** shown to be significantly better than TT alone for the treatment of uncomplicated CL in the New World
- *All AEs were classified as mild or moderate*
- Only one patient experienced a relapse between day 90 and day 180, supporting previous evidence that *reducing follow-up to day 90 for assessment of efficacy might be cost-effective*
- Limitation: no MLT monotherapy arm included in the study design
- Next step: a phase 3 study comparing the non-inferiority of the **combination of TT+MLT** against the current recommended treatment, sodium stibogluconate, and miltefosine monotherapy

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Thank you to the donors supporting DND*i*'s overall mission and the work on TT + MLT combination for CL

Programa de Estudio y Control de Enfermedades Tropicales, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
Ivan Dario Velez
Liliana Lopez
Juliana Quintero

Grupo de Estudios de Leishmaniasis y Malaria Instituto de Medicina Tropical Alexander von Humboldt Universidad Peruana Cayetano Heredia Lima, Perú
Alejandro Llanos Cuentas
Ana Pilar Ramos

Drugs for Neglected Diseases initiative (DNDi), Latin America
Marina Boni
Joelle Rode

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