TRANSLATION OF SCIENCE INTO POLICY OF NEW CONTROL TOOLS FOR THE MANAGEMENT OF AFRICAN VISCERAL LEISHMANIASIS

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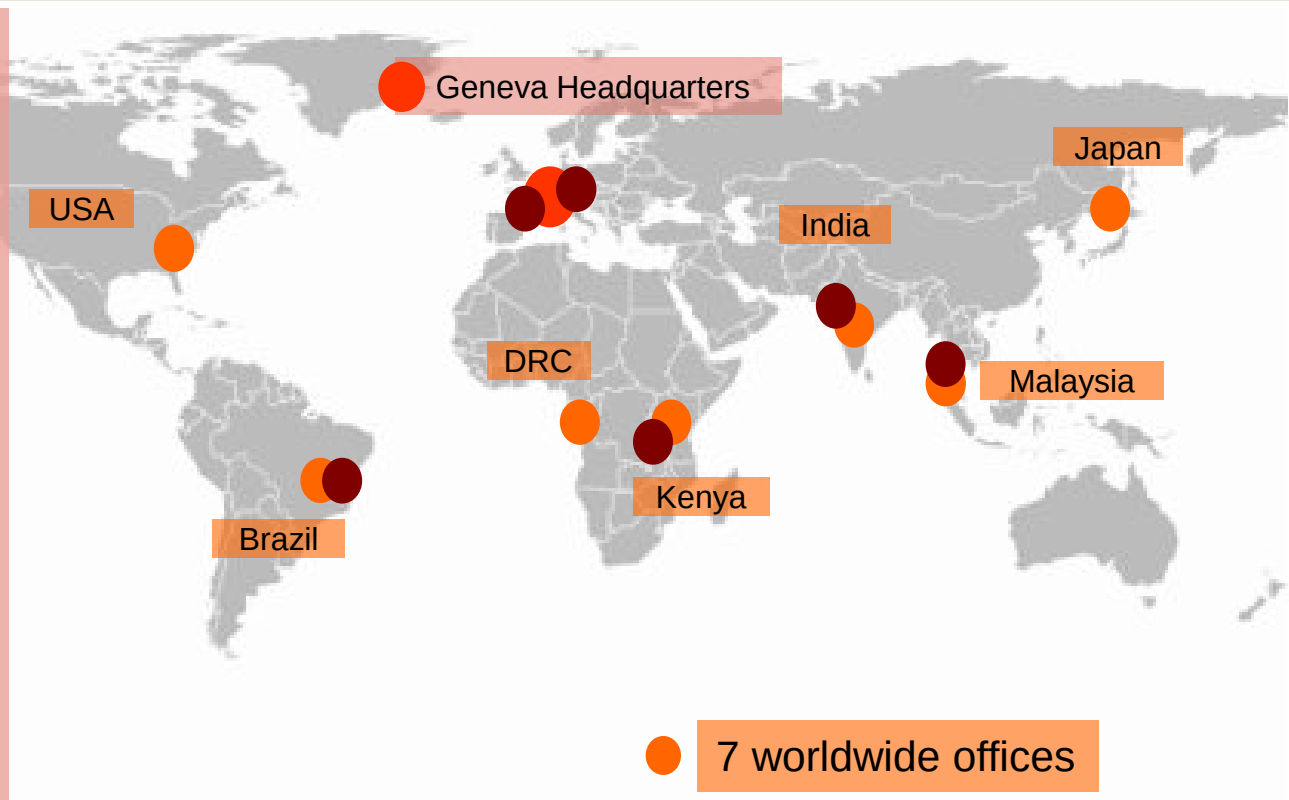
DND*i*'s model
Patient Needs-Driven & Innovative R&D Model

- Deliver **11 to 13 new treatments by 2018**
- Establish a **robust pipeline**
- Use and strengthen existing **capacity in disease-endemic countries**
- **Raise awareness** and advocate for increased **public leadership**

Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)

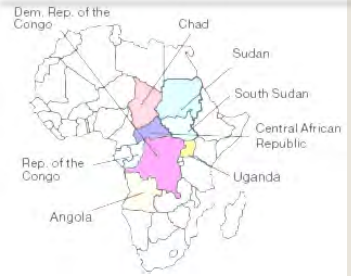


Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

VL

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

HAT



PLATEFORME REGIONALE DE RECHERCHE CLINIQUE THA
TRYPANOSOMIASE HUMAINE AFRICAINE
HUMAN AFRICAN TRYPANOSOMIASIS
REGIONAL PLATFORM FOR CLINICAL RESEARCH

CHAGAS

PLATAFORMA DE INVESTIGACION CLINICA EN ENFERMEDAD DE CHAGAS
CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

Major Role of Regional Disease Platforms:

- Defining patients' needs and target product profile (TPP)
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)

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The need in Visceral Leishmaniasis

- Oral, safe, effective, short course ,affordable

Table 4: Target Product Profile* for VL NCEs (as monotherapy)

	Optimal Target Profile	Minimal Target Profile
Target Label	VL and PKDL	VL
Spp	All species	L. donavani
Distribution	All areas	Either India or Africa
Target Population	Immunocompetent and immunosuppressed	Immunocompetent
Clinical Efficacy	> 95%	> 90%
Resistance	Active against resistant strains	
Safety and Tolerability	No AEs requiring monitoring	1 monitoring visit in mid/end - point
Contraindications	None	Pregnancy/lactation
Interactions	None - Compatible for combination therapy	None for malaria, TB, and HIV concomitant therapies
Formulation	Oral / im depot	Oral / im depot
Treatment Regimen	1/day for 10 days po/ 3 shots over 10 days*	bid for <10 days po; or >3 shots over 10 days
Stability	3 yrs in zone 4	Stable under conditions that can be reasonably achieved in the target region (> 2 yr)
Cost	< $10 / course (2008 dollar)	< $80 / course (2012 dollar)

* This is for primary VL only. PKDL, HIV co-infection and relapse case treatments may require longer treatment durations

DNDi short-term approach

For VL - antimonials

- drug resistance developing in Bihar
- 20 mg/kg/day for 30 days
- 4 weeks hospitalisation
- Renal and cardiac toxicity

Paromoycin: studied in 1996 /2000 &registered in India for VL in 2006 –21 days
Development of a combination with shorter course of existing treatments

SSG + PM 17 days vs PM 21 days and SSG 30 days

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Results showed comparable efficacy

Number of patients analyzeda	Number (%)cured	Treatment effect[b] (95% CI), p-value[c]
Six months follow-up:		
ITT: Complete Case Analysis[e]		
SSG: N = 359	337 (93.9)	2.5 (−1.3–6.3)
SSG & PM: N = 359	328 (91.4)	p = 0.198
PP: Complete Case Analysis[e]		
SSG: N = 357	336 (94.1)	2.8 (−1.1–6.6)
SSG & PM: N = 347	317 (91.4)	p = 0.157
ITT: Worst Case Analysis[f]		
SSG: N = 386	337 (87.3)	1.2 (−3.6–6.0)
SSG & PM: N = 381	328 (86.1)	p = 0.620
PP: Worst Case Analysis[f]		
SSG: N = 383	336 (87.7)	1.8 (−3.0–6.7)
SSG & PM: N = 369	317 (85.9)	p = 0.460
End of Treatment:		
ITT: Complete Case Analysis[e]		
SSG: N = 385	366 (95.1)	1.9 (−1.4–5.3)
SSG & PM: N = 378	352 (93.1)	p = 0.254

And no regional difference between the 4 EA countries

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SSG/PM as a new VL treatment: Development progress

2000s

Antimonials

2004

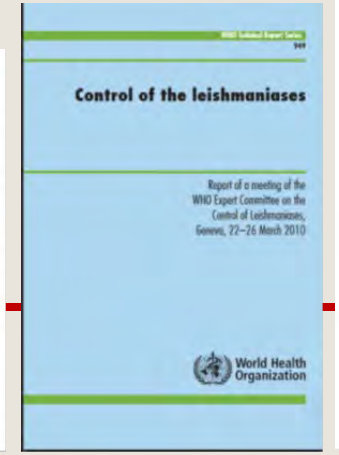
Initiation of SSG/PM study

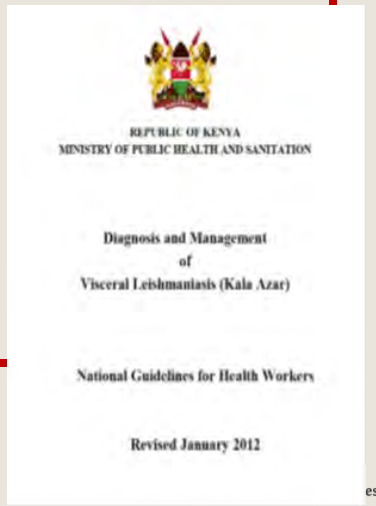
2009 completion of study

>1000 patients

2010 SSG/PM recommended in WHO Blue Book as 1st line therapy for East Africa


Sodium Stibogluconate (SSG) & Paromomycin Combination Compared to SSG for Visceral Leishmaniasis in East Africa: A Randomised Controlled Trial





es *initiative*

Translating clinical trial data to policy change: The PV effectiveness study

Only 1 prospective clinical study using the proposed new treatment

- Provide field evidence-based data documenting risk/benefit in larger patient group to help refining treatment guidelines
- Designed as part of a RMP
- Conducted with and by MoH, MSF, LEAP clinical sites

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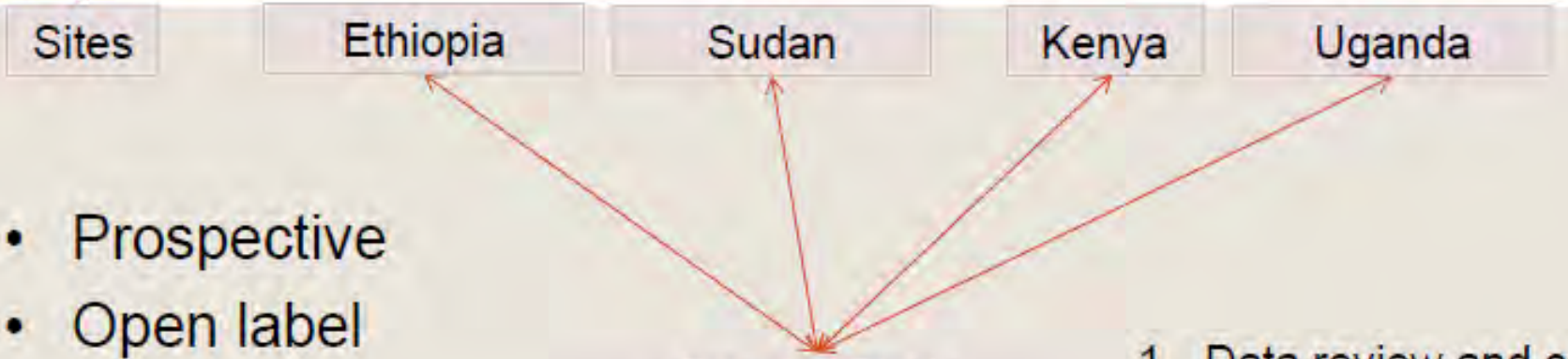
Project Design



- Prospective
- Open label
- Multicentre
- Observational
- Pharmacovigilance
- Effectiveness

Country Study Coordinator

1. Data review and collection
2. SAE
3. Supplies

KEMRI Data Centre / TCC

1. Data Management
2. Coding
3. Report preparation

Steering Committee

1. Safety review
2. Periodic update report

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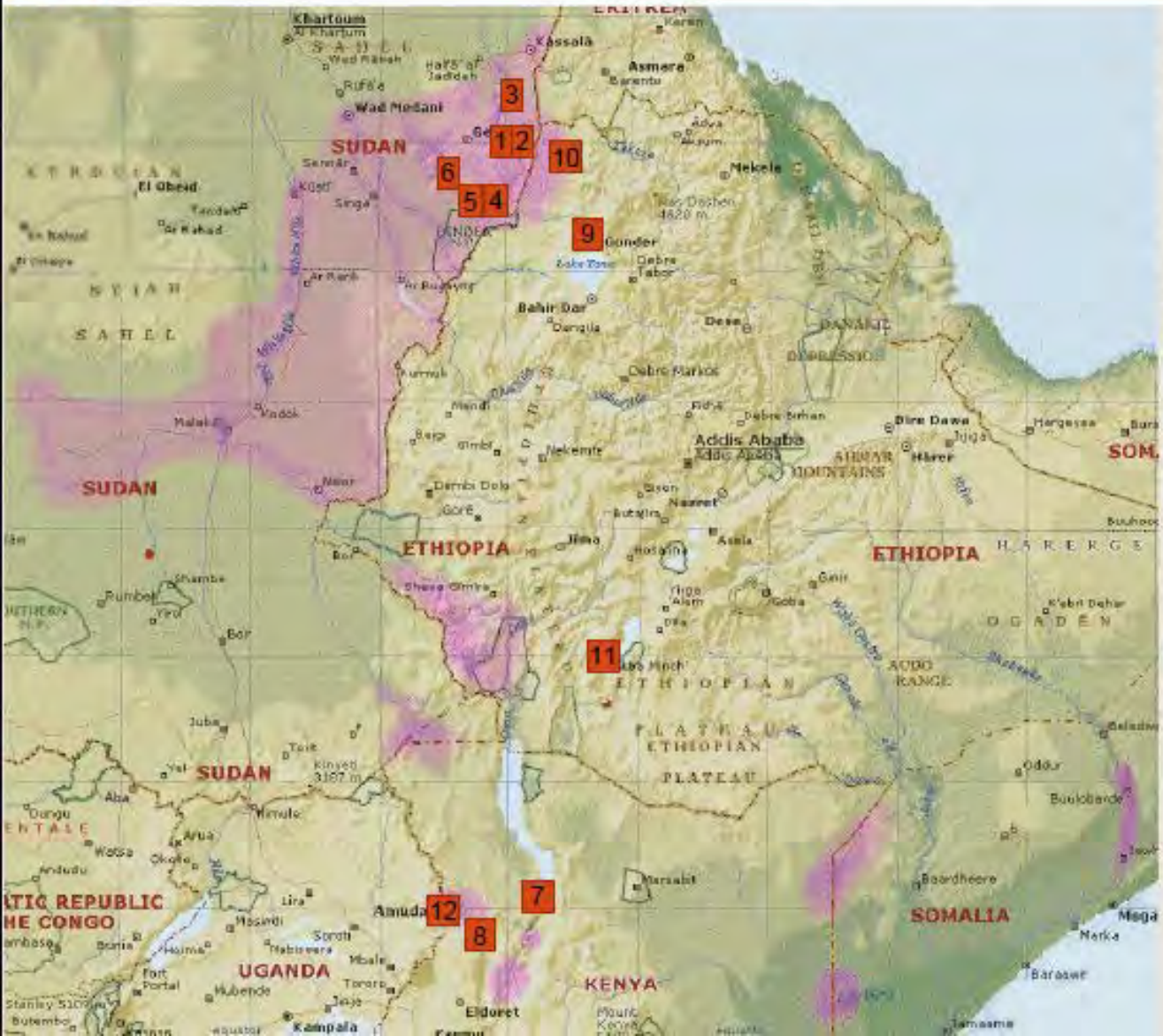
Participating Sites in SSG&PM



Sudan

1. Kassab Hospital - IED
2. Prof El Hassan Centre for Tropical Disease, Doka
3. Tabarakallah - MSF
4. Um el Kehr – MoH
5. Bazura – MoH
6. Elhawata – MOH

Kenya

7. Kimalel - KEMRI
8. Kacheliba – MSF, MoH/DNDi

Ethiopia

9. Gondar University Hospital,
10. Abdurafi
11. Arba Minch Hospital

Uganda

12. Amudat Hospital

FPI . Q3-2011
2948 patients recruited

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Various approval timelines

(WHO-EML)	SSG		Paromomycin		Ambisome		Miltefosine	
	EML	Regist	EML	Regist	EML	Regist	EML	Regist
Sudan	Yes	No	Yes	No (04/12)	Yes	No	?	No
Ethiopia	Yes	No	No	No (06/11)	Yes	No	Yes	No
Uganda	Yes	Yes	Yes	Yes (01/12)	No	tbc	No	No
Kenya	Yes	Yes	Yes	Yes (02/13)	Yes	No	No	No

	Adoption of SSG-PM in guidelines
Sudan	Guidelines revised, but not officially launched. To be printed once PV report is available.
Ethiopia	Guidelines revised, but waiting for PV report
Uganda	Guidelines revised, but not officially launched. Depending on new commissioner of NTD control program.
Kenya	Guidelines revised, launched and adopted in 2012.

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Access to treatment …

Table A6.2.
Price per visceral leishmaniasis treatment (January 2010)

Compound	Treatment regimen	Drug cost in US$[a]
L-Amb 10 mg/kg	1 day	126
L-Amb 20 mg/kg	2-4 days	252
Amphotericin B deoxycholate 1 mg/kg (alternating days)	30 days	20
MF 100 mg/day	28 days	65 - 150
PM 15 mg/kg/day	21 days	15
SSG 20 mg/kg/day	30 days	55,8
MA 20 mg/kg/day	30 days	59,3
L-Amb 5 mg/kg + MF 100 mg/day	8 days	88,2 – 109,5
L-Amb 5 mg/kg + PM 15 mg/kg/day	11 days	79
MF 100 mg/day + PM 15 mg/kg/day	10 days	30,2 – 60,7
(SSG 20 mg + PM 15 mg)/kg/day	17 days	44

[a] For a patient weighing 35 kg. Calculations for SSG and MF based on exchange rate of € 1 = US$ 1.41 (28 January 2010). Price range of miltefosine depends on order volume.
L-Amb=liposomal amphotericin B, MF=miltefosine, PM=paromomycin, SSG=sodium stibogluconate, MA=meglumine antimoniate

- WHO – procures SSG directly
- MSF and DNDi via IDA in provides SSG/PM in clinical trial settings
- Import when registered

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Use by WHO during VL outbreaks in South Sudan 2010-2011

	2010	2011
Primary Kala-azar	9166	10,413
Relapses	175 (2%)	571 (5,5%)
PKDL	965 (10,5%)	878 (8,4%)
Total	10306	11,862
Deaths	311 (3-3,5%)	252 (2-2,4%)

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Looking ahead – scientific challenges

Drugs	SSG	Ampho B Liposomal	Ampho B deoxycholate	MIL	PM sulphate	SSG+PM	LAB+SSG	LAB+MIL	PM+MIL
Clinical efficacy									
Asia	35-95% (depending on areas)	> 97% all regions	> 97%; single dose: > 96%	94-97% (India)	94% (India)	Not documented	> 97%	> 97%	> 97%
Africa	93%	33 - >97% (depending on areas)	Not fully established	72%	84%	91%	87%	79%	Not documented
Resistance	As high as 60% (India)	Not documented	Not documented	20% (Nepal)	Lab isolates (easily)	Lab isolates (easily)	Lab isolates	Lab isolates	Lab isolates (easily)

Priority to develop new tools <u>in</u> East Africa <u>for</u> the East African Region
For VL, PKDL and HIV-VL

Looking ahead: short-term clinical trials

Visceral Leishmaniasis and VL/HIV in Africa				
Study name	**SSG&PM Co-Administration Pharmacovigilance study**	**Fexinidazole Study (Fexi VL 001)**	**VL/HIV Co infection Study**	**Miltefosine Pharmacokinetics Study**
Counties and sites	16 sites (Sudan, Uganda, Kenya, Ethiopia)	1 site (Sudan)	2 sites (Ethiopia)	3 sites (Kenya, Uganda)
Clinical Phase	Phase IV	Phase II, PoC	Phase II/III (Planned to start mid-2014)	PK Study
Number of patients	3000	Up to 66 patients	up to 132 patients	Up to 30 patients
Partners	Leishmaniasis East Africa Platform (LEAP), Ministries of Health (MoH) of the LEAP countries, World Health Organization (WHO-TDR), IDA Foundation , i + solutions, London School of Hygiene and Tropical Medicine (LSHTM), MSF	Institute of Endemic Diseases (IEND), University of Khartoum, LSHTM, LEAP, BaseCon	LEAP, Addis Ababa University, Gondar University, MSF, LSHTM, Slotervaart Hospital, Utrecht University, Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; i+ solutions, Gilead, Paladin, Institute of Tropical Medicine, Antwerp (ITM-A)	ITM-A, LSHTM, MSF-Holland, College of Medicine and Health Sciences, University of Gondar Hospital

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Lessons learned

- Technical:
  - Anticipate with National Programs/MoHs as well as National Regulatory Agency the prerequisite for registration and procurement (LEAP)
  - Prepare for combination treatment
- Policy-wise:
  - Anticipate Risk Management Plan with possibly large field study
- Process-related:
  - Promote joint reviews of CTDs as well as joint site inspections

Thank you