Capacity Strengthening to Deliver a New FirstlineTreatment for Kala Azar in Eastern Africa: The Leading Role of the LEAP Platform

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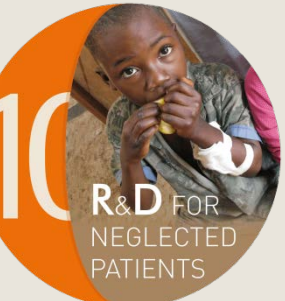
Presentation Outline

- Introduction: Neglected VL patients in Eastern Africa
- DNDi and the Idea of the Platform
- The LEAP Platform
- Responding to patient needs – the case of LEAP 0104
- LEAP Achievements & Challenges
- Conclusion



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Bridging The R&D Gap:
The Reality for Neglected Patients…

- Poorest of the poor
- Living in remote areas
- Socioeconomic burden on family and community
- Marginalized & voiceless patients

VL In Eastern Africa

- VL is a poverty-related disease
- In Africa primarily affects children (over 60%)
- If untreated, VL is fatal
- Population displacements have exacerbated the spread of the disease
- Field-relevant treatments are scarce

(Photo courtesy of Prof. A Hailu)

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DNDi –The Idea of The Platforms Started in 2003

1st DNDi Africa meeting

- 7-9 May 2003, Nairobi: 18 African countries, 71 participants
- Neglected, marginalized, forgotten, invisible diseases
- Consensus conclusion: more action, fewer words
- Desire to collaborate to solve many health crises plaguing Africa
- For diseases urgently needing improvement of treatments: VL, HAT
- DNDi officially created the LEAP Platform in August 2003 in Khartoum, Sudan

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LEAP

LEISHMANIASIS EAST AFRICA PLATFORM

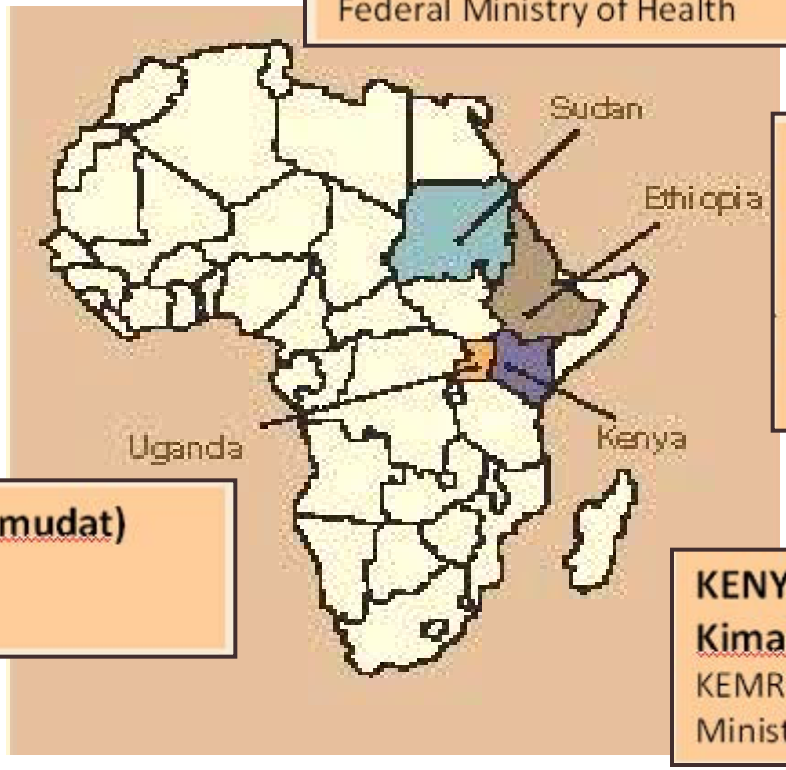
60 members. 4 countries. VL experts. Physicians with expertise to run clinical trials. Researchers. Health professionals. Representatives from drug registration authorities in disease endemic areas. NGOs.

Leishmaniasis East Africa Platform (LEAP)

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

A group of scientists and institutions working on developing clinical trial capacity to bring new treatments to patients

SUDAN: 3 sites (Kassab, Dooka, Um El Kher)
Univ. of Khartoum
Federal Ministry of Health



ETHIOPIA: 2 sites (Gondar, Arba Minch)
Addis Ababa Univ.
Gondar Univ.
DACA
Ministry of Health

UGANDA: 1 site (Amudat)
- Makerere Univ.
- Ministry of Health

KENYA: 2 sites (Nairobi, Kimalel)
KEMRI
Ministry of Health

LEAP collaborates with
DNDi, MSF, IOWH – India, IDA, TDR and industry partners in Visceral Leishmaniansis (VL) R&D work in East Africa

LEAP Members

LEAP Objectives

- **Evaluate, validate and register improved treatment options** for VL in the Eastern African region (Ethiopia, Kenya, Sudan and Uganda)
- Provide **capacity strengthening for treatment**, evaluation and clinical studies in the region

Advantages of LEAP

LEAP at inception was envisaged to:

- Be a true example of **South-South collaboration**
- ***Join efforts*** with regional health and regulatory authorities, in addressing the high burden of disease through research and community engagement
- Give priority to address the ***needs of patients***
- ***Develop joint proposals***
- Seek ***joint funding*** for its activities

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Advantages of LEAP Cont'd

Such collaboration allows LEAP to:

- **Strengthen existing capacities** for conducting trials in Eastern Africa
- **Eliminate duplication of effort** – time taken to get meaningful results minimized.
- ***Accelerate registration*** of much needed new VL drugs in all member countries
- To be a ***trusted reference group*** by the community and governments
- ***Efficiently translate research results into policy***

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Responding to patient needs – the case of LEAP 0104 clinical trial

LEAP 0104

A multi-centre comparative trial of efficacy and safety of sodium stibogluconate (SSG) versus paromomycin (PM) versus combination of SSG and PM as the first line treatment for visceral leishmaniasis in ***Ethiopia***, ***Kenya*** and ***Sudan***

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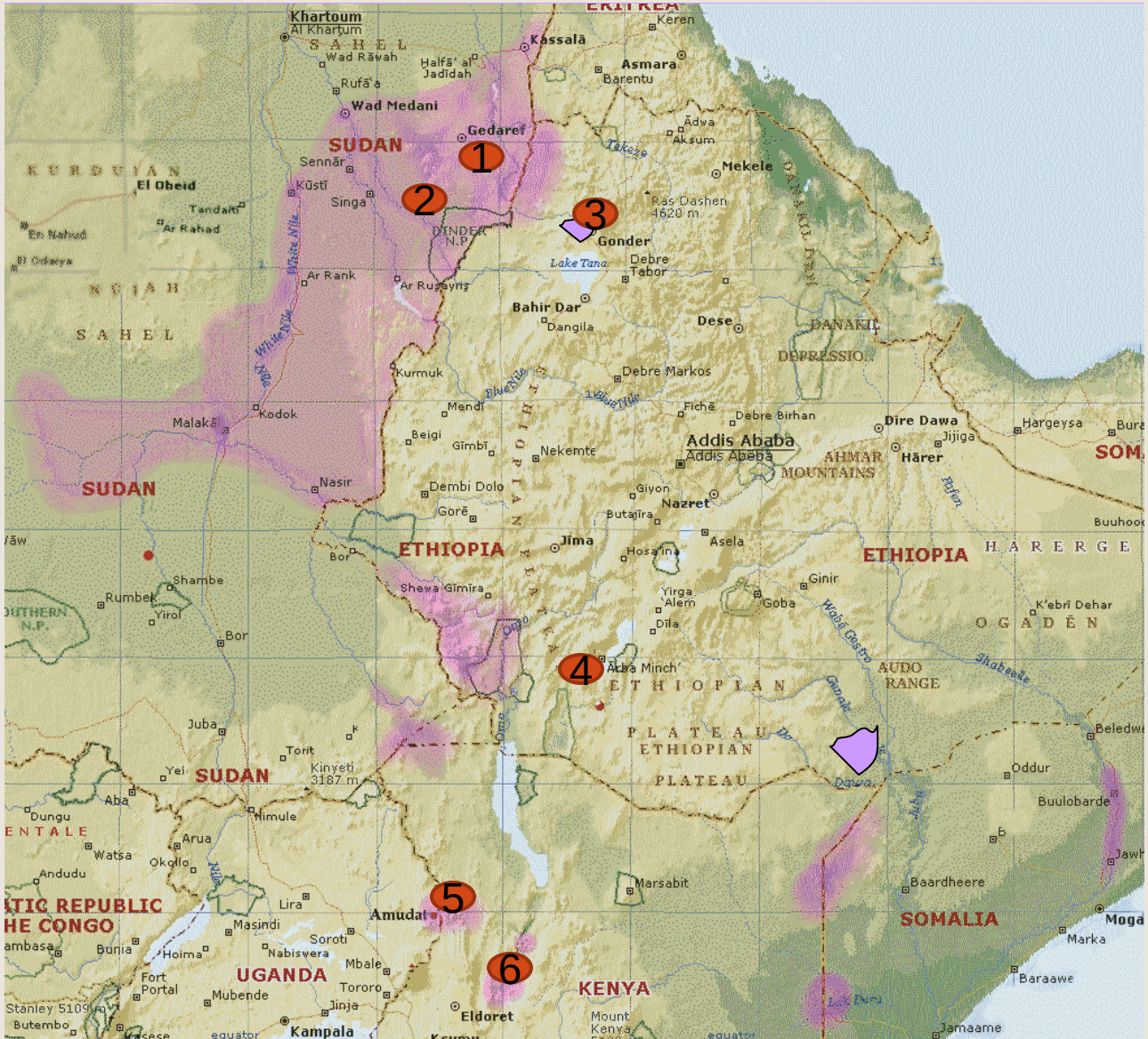
LEAP 0104 Clinical Trial Sites



1 Kassab Hospital, University of Khartoum, *Sudan*

2 Um el Kehr centre, MSF-Holland, *Sudan*

3 Gonder Hospital, Gonder University, *Ethiopia*

4 Arba Minch Hospital, Addis Ababa University, *Ethiopia*

5 Amudat Hospital, Makerere University, *Uganda*

6 Kimalel Hospital, KEMRI, *Kenya*

7 *Centre for clinical Research, KEMRI, Nairobi*

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

LEAP 0104: Objectives of the trial

- **To assess the efficacy and safety of SSG 30 days** alone in the treatment of patients with VL.
- **To assess the efficacy and safety of PM 21 days** alone in the treatment of patients with VL.
- **To assess the efficacy and safety of SSG and PM as a combination course of 17 days** in the treatment of patients with VL.

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SSG&PM: Sodium Stibogluconate & Paromomycin

Results

Analysis of SSG&PM: Efficacy outcomes

	ITT		PP	
	SSG (N = 359)	Combination (N = 359)	SSG (N = 357)	Combination (N = 347)
Efficacy at 6 months follow-up, n (%)	337 (93.9)	328 (91.4)	336 (94.1)	317 (91.4)
Unadjusted difference between SSG and Combination (95% CI)	2.51% (-1.31 to 6.33%)		2.76% (-1.07 to 6.60%)	
Test of difference between treatment efficacy: p value*	0.198		0.157	
Test of difference across centres, after adjustment for treatment: p value*	0.337		0.286	
Test of difference between adults and children after adjustment for treatment: p Value*	0.122		0.080	

- Reasons for exclusions from PP analysis include: Low HB, Low WCC, incorrect treatment given, expired medication given

*p-value from likelihood ratio test, comparing models with and without variable being tested

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LEAP Achievements & Challenges

Achievements

Clinical Trials

- SSG+PM; a ***new improved combination treatment*** for VL
- ***Completion of LEAP 0104A & B*** SSG+PM multi-centre clinical trial; i*ncluding PK for SSG & PM*
- ***Single high dose of AmBisome*** for the treatment of primary VL (AmBi 0106); *including PK/PD for AmBisome*

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Achievements Cont'd

Clinical Trials

- AmBisome combination trial in Eastern Africa ***(LEAP 0208 SSG+PM, SSG+AmB, MILT+AmB Including PK/PD)***
- Study of ***rapid diagnostic tests***
- SSG +PM (combo) ***PV study completed***
- Safety and efficacy of ***Fexinidazole Phase II*** for primary VL, ongoing in Sudan

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Achievements Cont'd

- **Capacity Strengthening**
  - ***Research capacity strengthening*** in Ethiopia, Kenya, Sudan and Uganda in the following domains: *(Clinical trials, Communications, Infrastructure*)

Arba Minch Research & Treatment Centre, Ethiopia

Ethiopia

Gondar, Clinical Trial Center before rehabilitation

Arba Minch, before rehabilitation

Gondar New Site

Arba Minch new lab

Achievements Cont'd

- **Capacity Strengthening**
  - ***Training across the LEAP*** (Short-term and post graduate)

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Trainings: Short-term

Training	No. of Participants
Good Clinical Practice (GCP)	354
Pharmacovigilance (PV) Training	104
PPD GCP/GCLP	95
Audiometry	26
VL Guideline (Kenya)	55
Urine LEISH Antigen Elisa standardization training	15
Lab Safety & Refresher Parasitology Course	14
From Molecule to Medicine	4
Human Subjects Protection (HSP/GCP) TOT Programme	5
Clinical Monitors course – “Back to Basics”	2
DSMB & Monitor’s training	30

Trainings: Post Graduate

Training	No. of Participants
Diploma in Medicine	1
Bachelors (Lab, Nursing, Pharmacy)	10
MSc	12
MPH	1
PhD	2

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South-South & North-South Collaboration

- Bringing together research institutions, academia, MoH and NGO's (Key players)
- Influencing policy at both national and international levels

Achievements Cont'd

- **Data Center**
  - Developed off-line OpenClinica
  - Facilitate DM for multiple clinical trial

- **Community Benefit**
  - **Over 7,000 VL patients treated**
  - Increased awareness in the **community**, improved access reduction in **morbidity**, early **reporting** to health facilities
- **Financial**
  - Implementation of Good Financial Practice (GFP)

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Achievements Cont'd

PUBLICATIONS

- ***Safety and Efficacy of Single Dose Versus Multiple Doses of AmBisome® for the Treatment of Visceral Leishmaniasis in Eastern Africa: A Randomised Trial***, E.A.G. Khalil, T. Weldegebreal, et al., *PLoS Negl Trop Dis.*, January 2014
- ***Validation of Two Rapid Diagnostic Tests for Visceral Leishmaniasis in Kenya,*** *J. Mbui, M. Wasunna, et al., PLoS Negl Trop Dis.*, Sept., 2013
- ***Stibogluconate (SSG) & Paromomycin Combination Compared to SSG for Visceral Leishmaniasis in East Africa: A Randomised Controlled Trial,*** *Ahmed Musa, Eltahir Khalil et al.,* PLoS NTDs, 6(6): e1674, June 2012
- ***Single-dose liposomal amphotericin B (AmBisome®) for the treatment of Visceral Leishmaniasis in East Africa: study protocol for a randomized controlled trial****, Raymond Omollo, Neal Alexander et al., Trials 12(1):166 (2011) PMID 21718522.* Licensee BioMed Central Ltd
- ***Geographical Variation in the Response of Visceral Leishmaniasis to Paromomycin in East Africa: A Multicentre, Open-Label, Randomized Trial ,*** Hailu A, Musa AM, et al, PLoS Negl Trop Dis 4(10):e709.doi:10.1371/journal.pntd.000070
- ***Paromomycin for theTreatment of Visceral Leishmaniasis in Sudan: A Randomized, Open-Label, Dose-Finding study,*** *Ahmed Musa, Brima Younis et al.,* PLoS Negl Trop Dis 4(10): e855.doi:10.1371/journal.pntd.0000855, 2010

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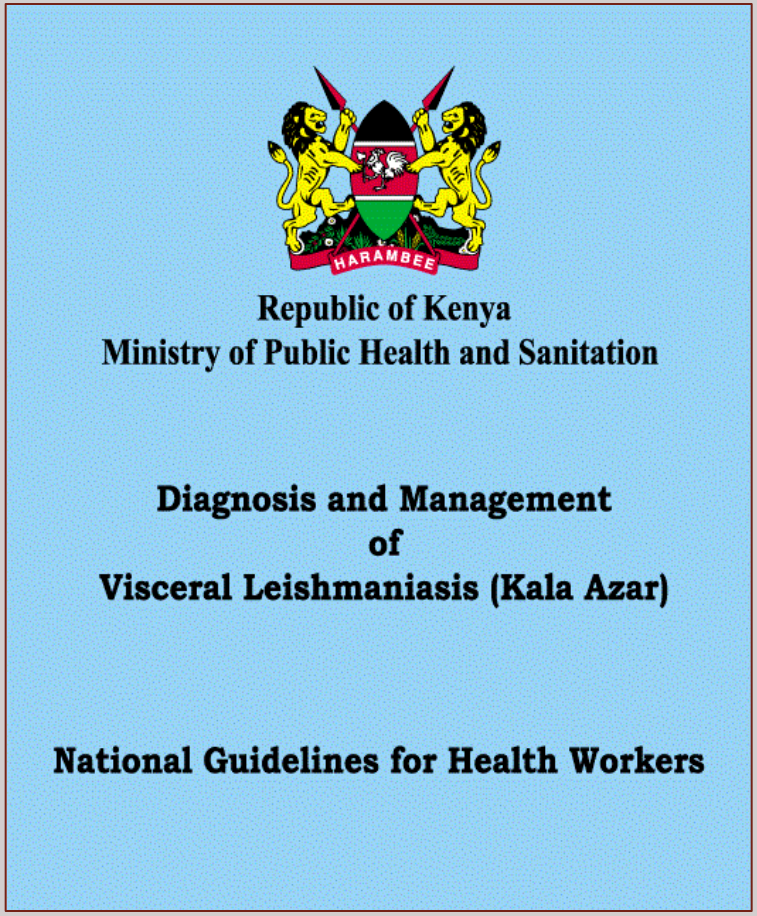
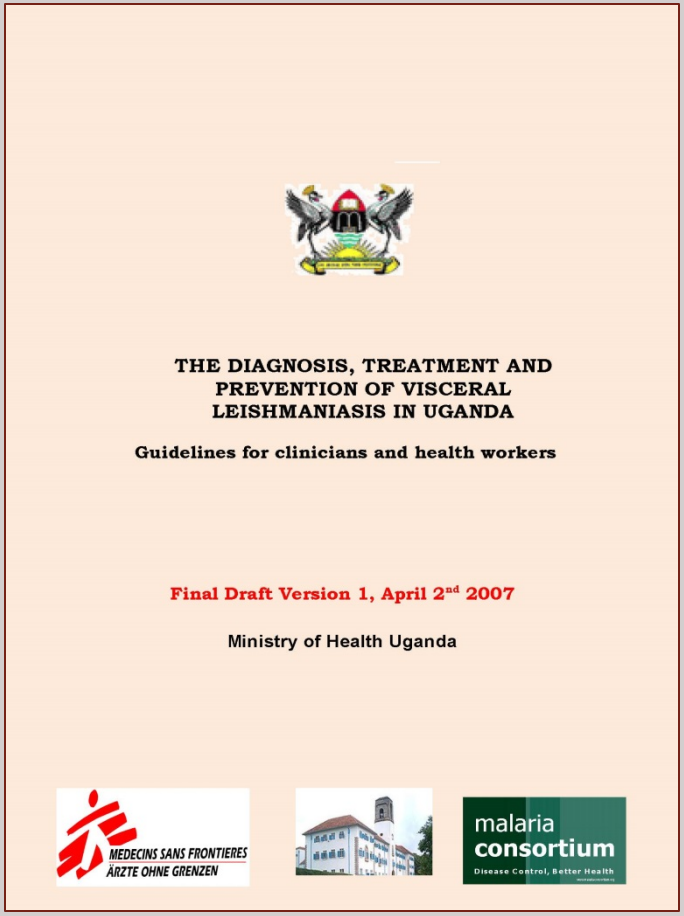
Policy Change

The National VL Guidelines



Kenya's VL guidelines launched September 2012



Uganda VL guidelines

LEAP: Advocacy

Events

Promised support for our activities by committing funding for NTDs in the 2014/2015 Health Budget

Prof. Fred Segor, PS Health, Kenya

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Challenges

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Challenge to Conduct Clinical Trials in Very Difficult Settings

- Access to Sites
- Status of Infrastructure
- Staff Limitations

JS

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Conclusion

- Treatment for VL not yet optimal. Need more research
- Patient needs of efficacious, safe oral drug for VL is still unmet
- LEAP Platform's 10 years have been a success. The next 10 years will be even greater delivering oral treatment to neglected patients

- **South-South, South-North** collaboration is possible
- **Equal partnerships** is key to success
- VL disease endemic areas in Africa can pull **resources, infrastructure, expertise** for the benefit of the neglected communities
- Clinical Research at **international standards** is possible in remote disease endemic areas in Africa
- **Early involvement of MOH** in clinical trials leads to faster policy change.

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THANK YOU! ASANTE SANA

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