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Session 2 title: Infectious and Neglected Diseases

Drug development for Kinetoplastids

*“Treatment modalities for Visceral Leishmaniasis (Kala Azar) under
field routine program conditions”*



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DNDi Symposium



Overview:

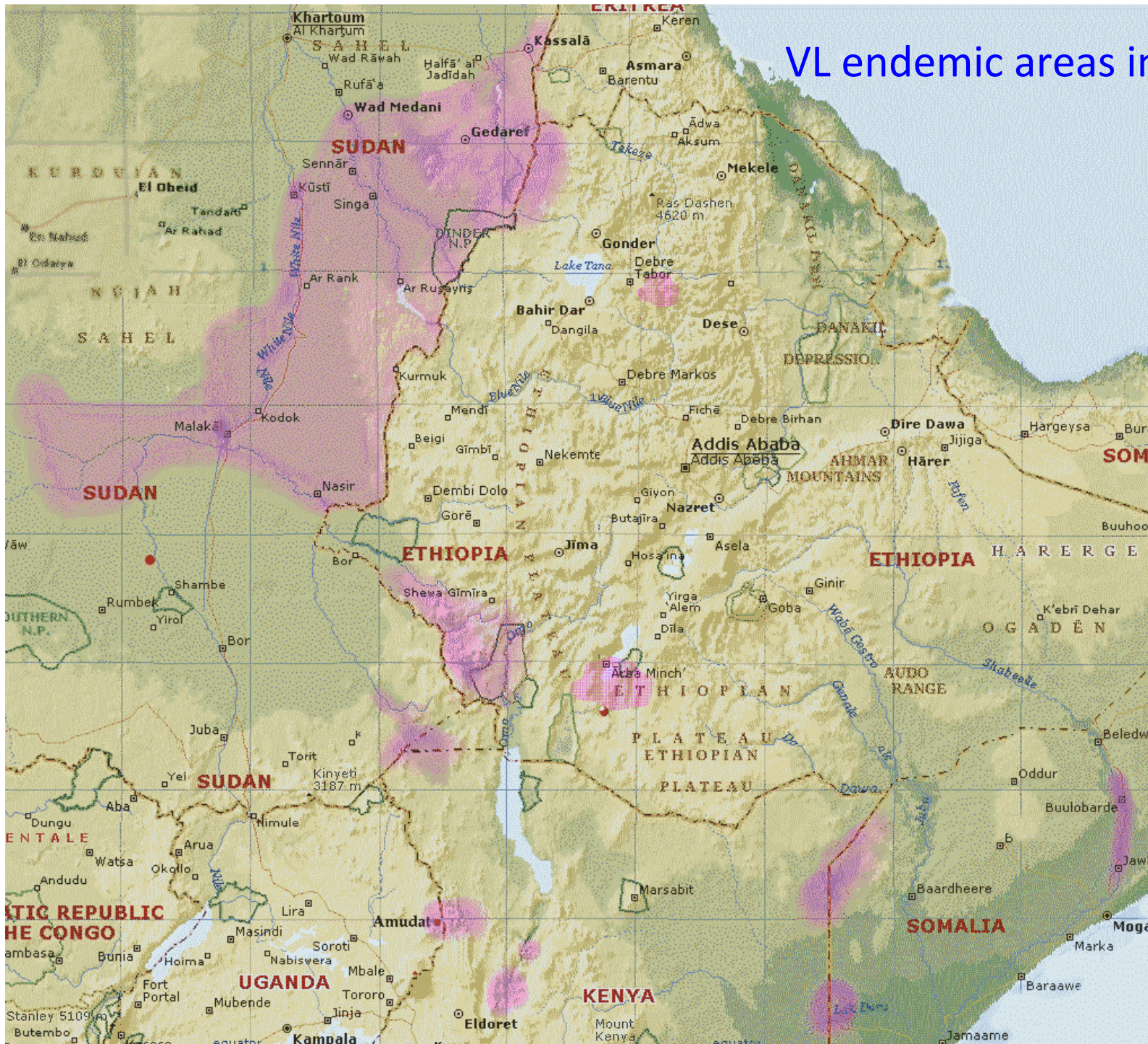
Since 1989, Médecins Sans Frontières (MSF) has provided medical humanitarian assistance of Visceral Leishmaniasis in Sudan, Ethiopia, Uganda, Kenya, Somalia, India and Bangladesh.

Most of these areas are characterized by extreme isolation, insecurity and poverty

Between 1989 and 2011 MSF treated over 100,000 patients with significant improvements in treatment outcomes

This has been largely done over the years through operational research, with proper monitoring and follow up of patients, publishing & capitalizing these treatment results.

VL endemic areas in East Africa



MSF History in East Africa: Response to KA outbreaks

MSF kala-azar interventions in East Africa were all in response to epidemic outbreaks:

- 1989 Western Upper Nile, Southern Sudan
- 1995 Eastern Upper Nile, Southern Sudan
- 1996 Gedaref State, Eastern Sudan
- 1997 North-west Ethiopia
- 2002 Eastern Upper Nile and North-west Ethiopia
- 2009-2011: Major outbreak response in Jonglei and Upper Nile States in South Sudan...

MSF has followed the epidemics as they spread like bushfires across the endemic belt in Sudan/Ethiopia

Characteristics of VL-endemic areas in East Africa

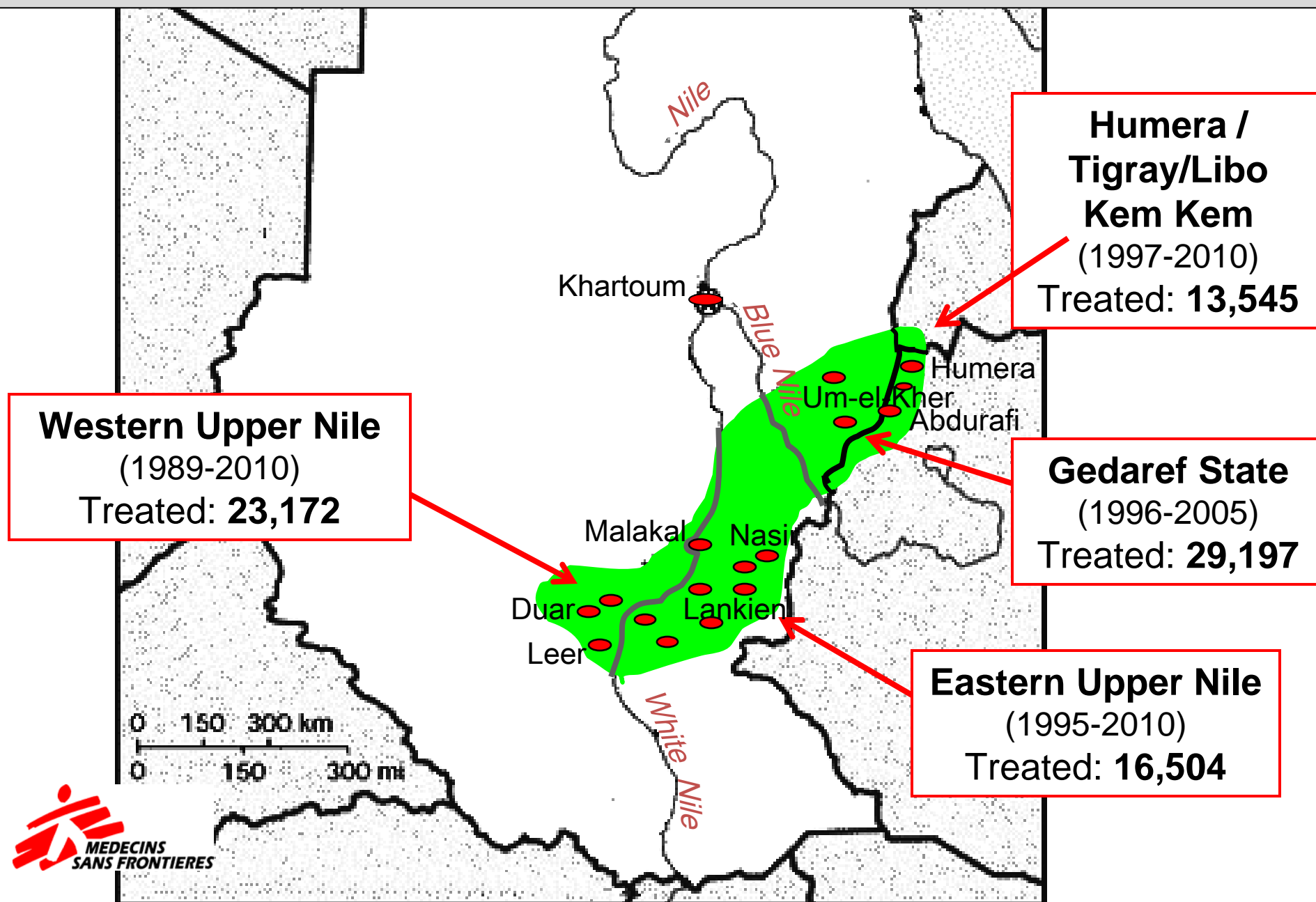


- Disease endemic regions are extremely remote and isolated; lack of infrastructure
- Extreme poverty
- Active conflict or insecurity
- Lack or absence of health care infrastructure

- Non-specific signs and symptoms
→ large number of individuals
need to be screened to identify
patients



VL cases treated by MSF in Sudan & Ethiopia, 1989 – 2010

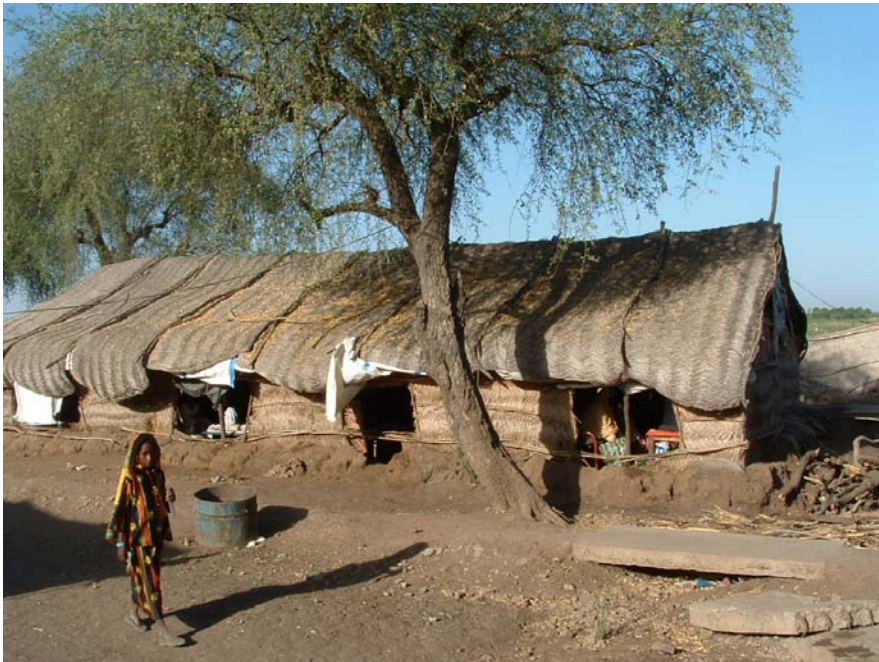


Treatment centres

Hospital (*Humera, north-west Ethiopia*)



Field Hospital (*Um-el-Kher, eastern Sudan*)

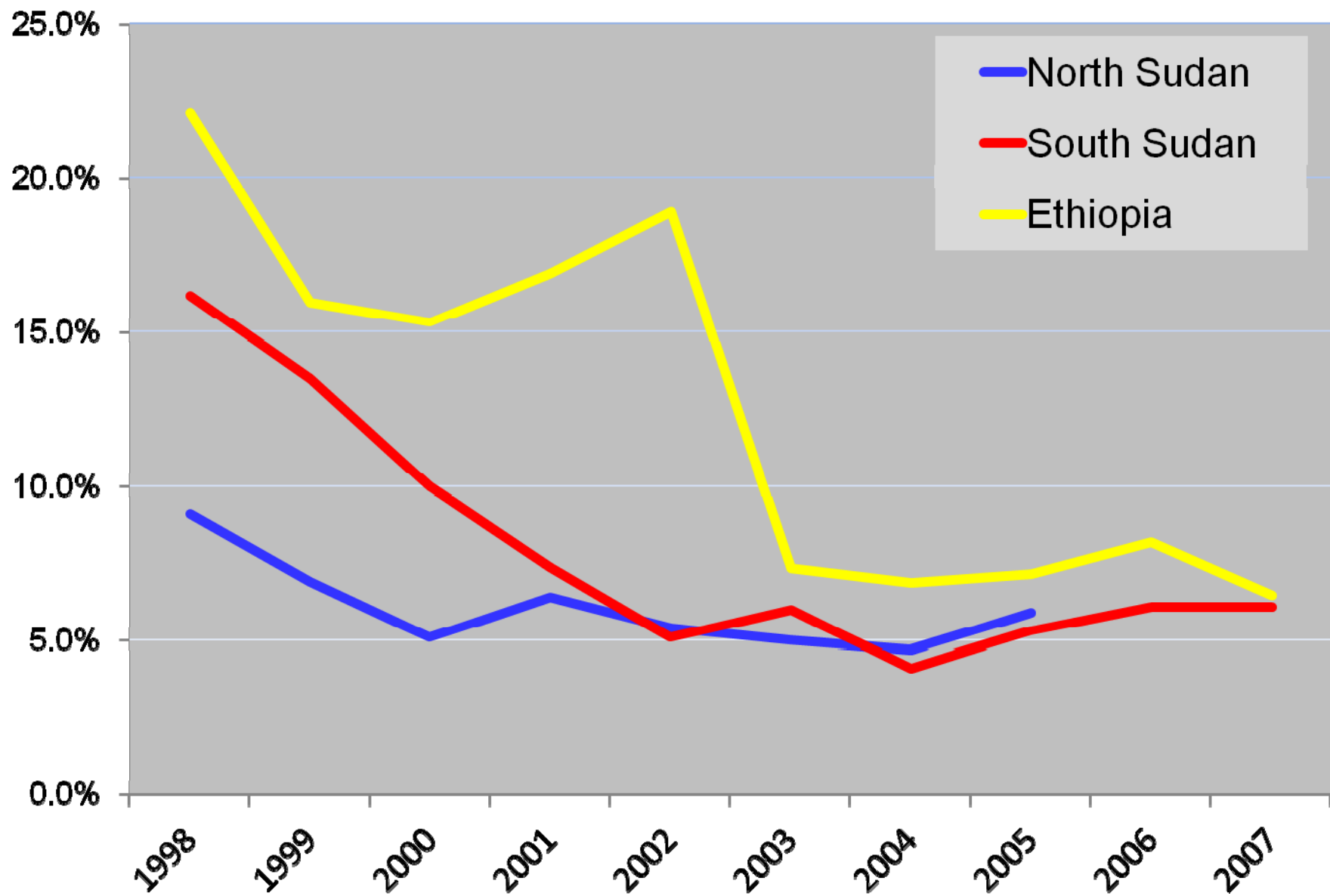


Treatment centres

Under the trees
(Lankien, southern Sudan)



Primary VL Death Rates (1998 – 2007)



Improved treatment outcomes

Field operational research:

- Effectiveness of generic drugs (reduced costs)
- New (safer) drugs and treatment regimens
- Improved treatment of opportunistic infections and complications (e.g. severe malnutrition)

Despite the very high HIV co-infection rate in Ethiopia (up to 35% of VL cases), and the difficulties in treating HIV/VL co-infection (drug unresponsiveness, drug toxicity), treatment outcomes have improved dramatically over the years



Decentralised diagnosis & treatment

Main factor has been the introduction of the rK39 rapid test, allowing decentralization of diagnosis and treatment, thus improving access to early treatment of VL

AmBisome (20-30 mg/kg IV) second line treatment for severe VL at Hospital and PHC level

Short treatment schemes



Paromomycin / SSG short-course combination therapy in southern Sudan

Treatment facilities suddenly overwhelmed during an epidemic outbreak of VL in a very remote and resource poor setting

Introduction of short-course combination therapy, in order to:

- increase patient turnover, and decongest treatment capacity
- reduce risk of outbreaks of opportunistic infections
- improve treatment outcomes

Regimen:

17 days Paromomycin (15 mg/kg/d),
combined with 17 days SSG (20 mg/kg/d)

Exclusion Criteria:

- Severely ill VL (AmBisome)
- 2002-03: WCBA (SSG)
- 2004: Pregnant women (AmBisome)



Methodology

Retrospective analysis of 4,263 primary VL patients treated between 2002 and 2005 in southern Sudan

- 1,178 patients treated with 30 days SSG monotherapy
- 3,081 patients treated with 17 days Paromomycin / SSG combination therapy



Patient outcomes per treatment group in Southern Sudan

Treatment	SSG	PM / SSG	<i>P-value</i>
No. of primary VL cases	1,178	3,085	
Initial cure (%)	92.4	97.0	< 0.001
Death (%)	7.6	3.0	< 0.001
Vomiting (%)	28.8	27.5	0.39
Diarrhoea (%)	38.5	26.3	< 0.001
Bleeding (%)	4.4	2.8	0.006
Mean weight gain (%)	5.1	3.3	< 0.001
Spleen regression on discharge (%)	82.1	84.0	0.52

Conclusion: in remote field settings, 17 days of PM/SSG combination gives better survival and initial cure rates than 30 days of SSG monotherapy. DNDi sponsored phase III study has extended these findings: treatment now recommended as first line by WHO expert committee in Sudan

MSF KA Program in India 2007-2011:

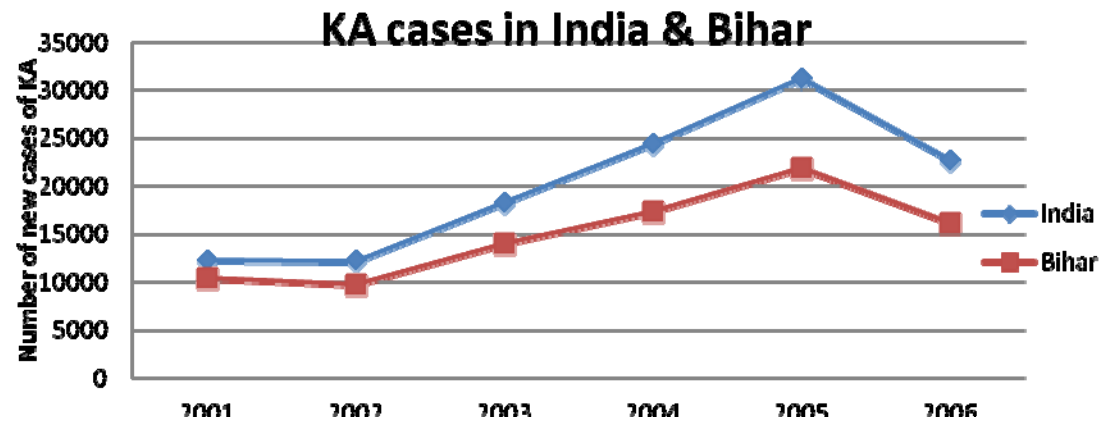
Treatment for Visceral Leishmaniasis (VL) under routine conditions in Vaishali, Bihar, India



MSF-VL project in Bihar



- Second poorest state of the country.
- Around 60 – 75% VL cases of India are in Bihar
- MSF decided to start a project to push for innovation in treatment



Objectives

- To monitor tolerability and safety of first line AmBisome®, at a total dose of 20mg/kg body weight, under routine programme conditions (5mg 4 days).
- To monitor effectiveness of AmBisome®.



Continued...

- Safety monitoring
 - Clinical assessment



- Effectiveness end points:
 - At the end of treatment (day 10): all patients
 - Final cure at 6 months
 - Clinically well
 - If clinically suspected, parasitological clearance

End-of-Treatment Effectiveness

- Total Number of Primary VL patients treated from July 2007 until August 2011: 7,140
- Initial cure rate at discharge= 98.7%
- Defaulter rate= 0.8%
- Death rate= 0.5%
- Relapse rate remains low (1.2%).



Next steps for 2011-14: New treatment modalities in India



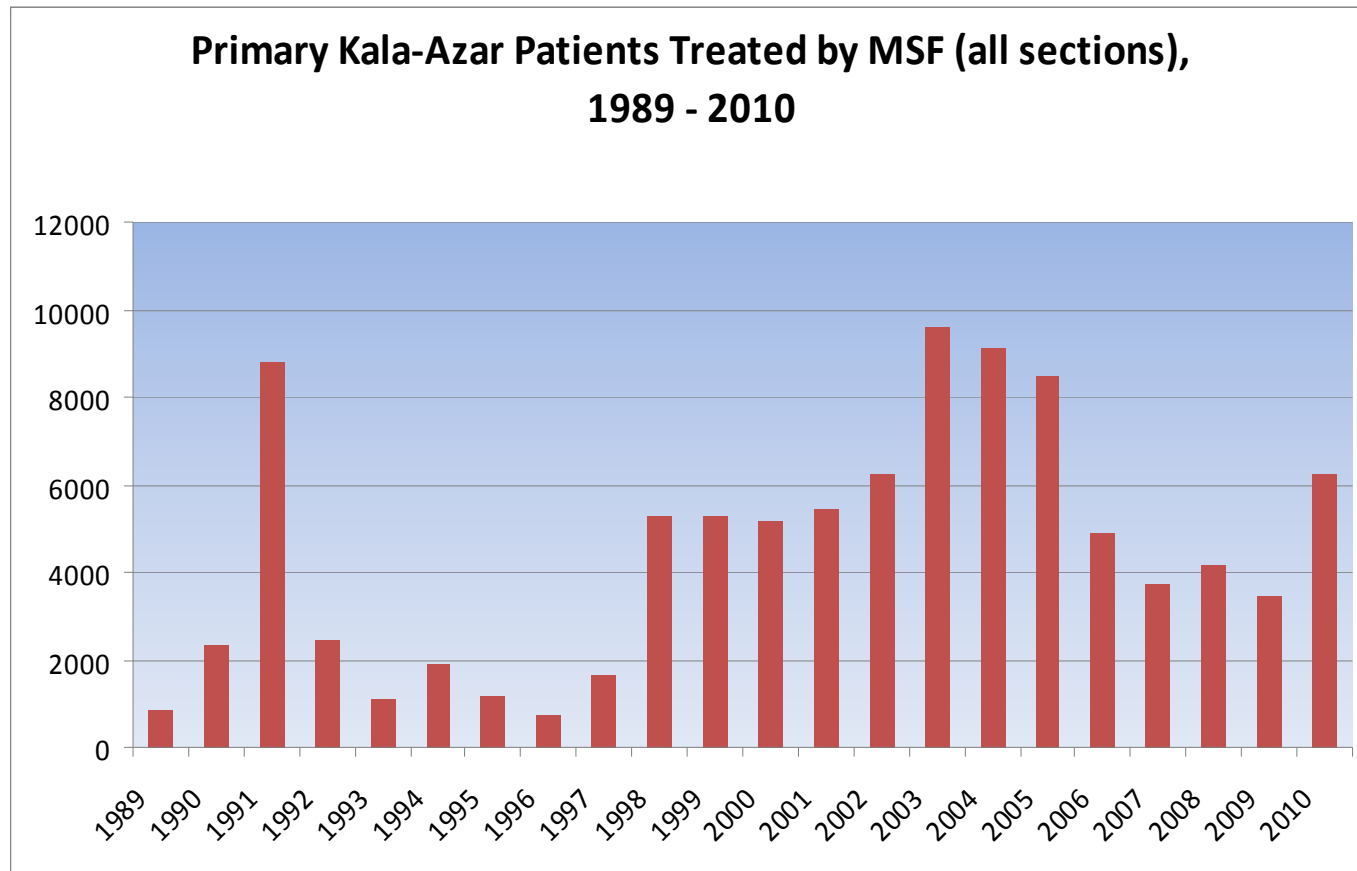
**DNDi+MSF+Indian MoH+ICMR will jointly implement a pilot project to monitor safety and effectiveness of the new treatment modalities under routine program conditions:
(Feasibility at PHC level)**

- **Single dose AmBisome® (10 mg/kg)**
- **Combination with AmBisome® and Miltefosine (single dose AmBisome followed by 7 days MF)**
- **Miltefosine and Paromomycin given over 10 days**

New treatment modalities in Bangladesh

- **AmBisome short course 15 mg for PVL patients**
- **AmBisome short tx course for PKDL patients**

Summary of 2 decades of MSF's work



North Sudan 28.328

South Sudan 40.590

Ethiopia 14.357

Somalia 3.903

Kenya 2.065

Uganda 2.437

Bangladesh 402

India 6.121

TOTAL 98.203

From 1989 until 2011 MSF has treated more than 100,000 patients in East Africa and Asia



¡GRACIAS!