Seeking for Alternative treatments for Visceral Leishmaniasis

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ICOPA, 14th Aug 2014

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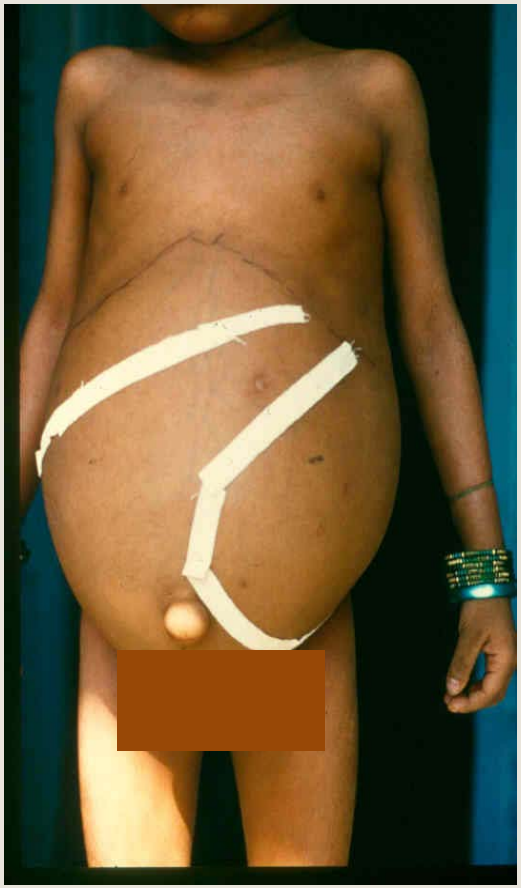
Visceral leishmaniasis reported cases (average 2004-08) and estimates



	Cases reported/y	Estimated annual
America	3 661	5 000 to 7 000
West Africa	-	-
East Africa	8 569	30 000 to 40 000
Mediterranean	875	1 500 to 2 000
Middle East & Central Asia	2 496	5 000 to 7 500
Indian Subcontinent	42 619	160 000 to 320 000
	58 220	**201 500 to 376 500**

100% fatal if untreated
Treatment toxic, expensive, long duration

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Aims of the DNDiVL Program

- In the Near Term
  - Register combinations for East Africa
  - Provide ammunition for policy change in India and LatAm
  - Determine suitability of miltefosine as an oral combination partner in East Africa
- Longer Term
  - Develop new oral drugs as quickly as possible by
    - Bringing new candidates for clinical development
    - Increasing sites and recruitment rates – ‘LEAP v2.0’
  - Determine role of asymptomatics & PKDL patients as disease reservoir
  - Increase Discovery pipeline

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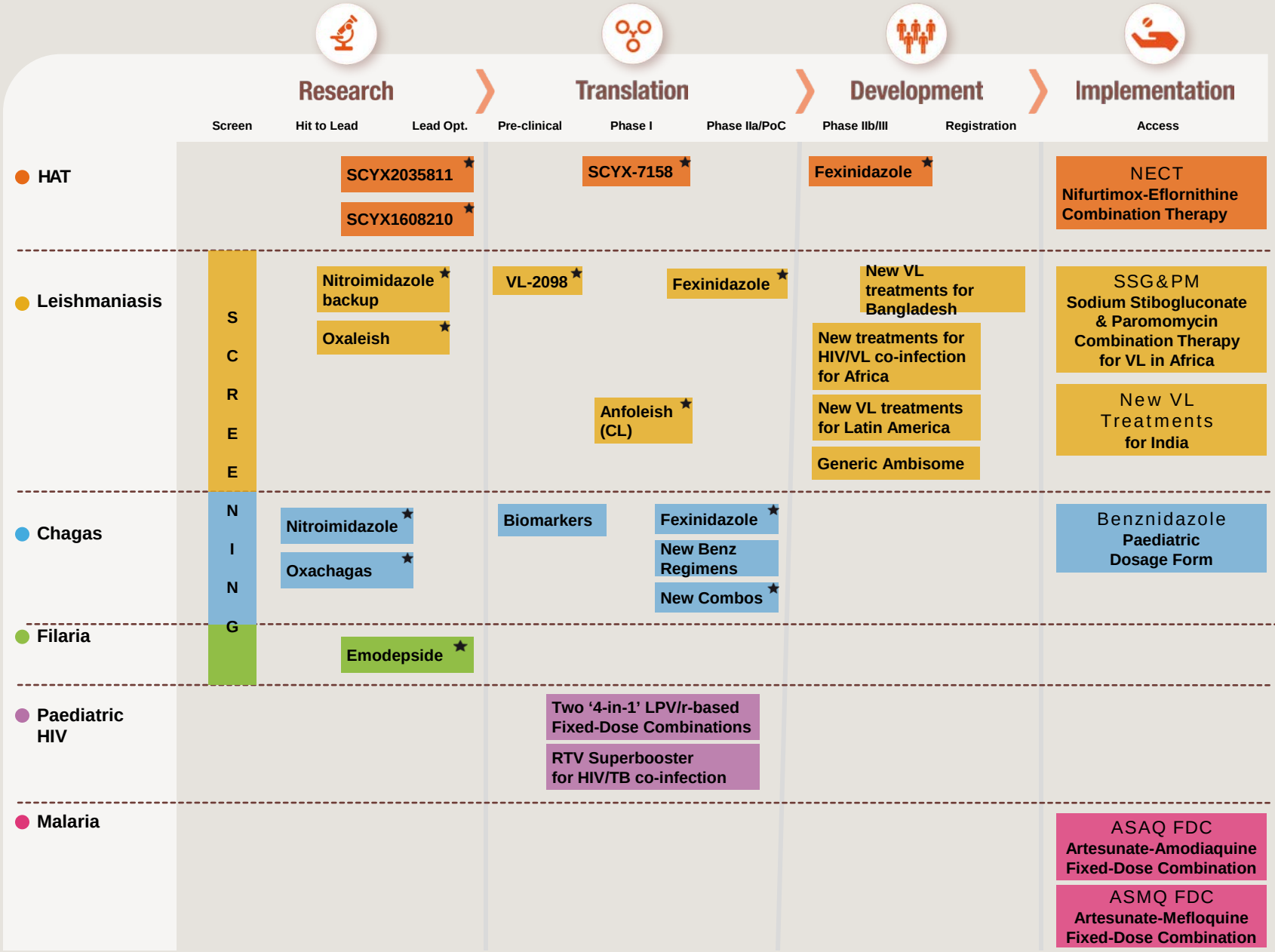
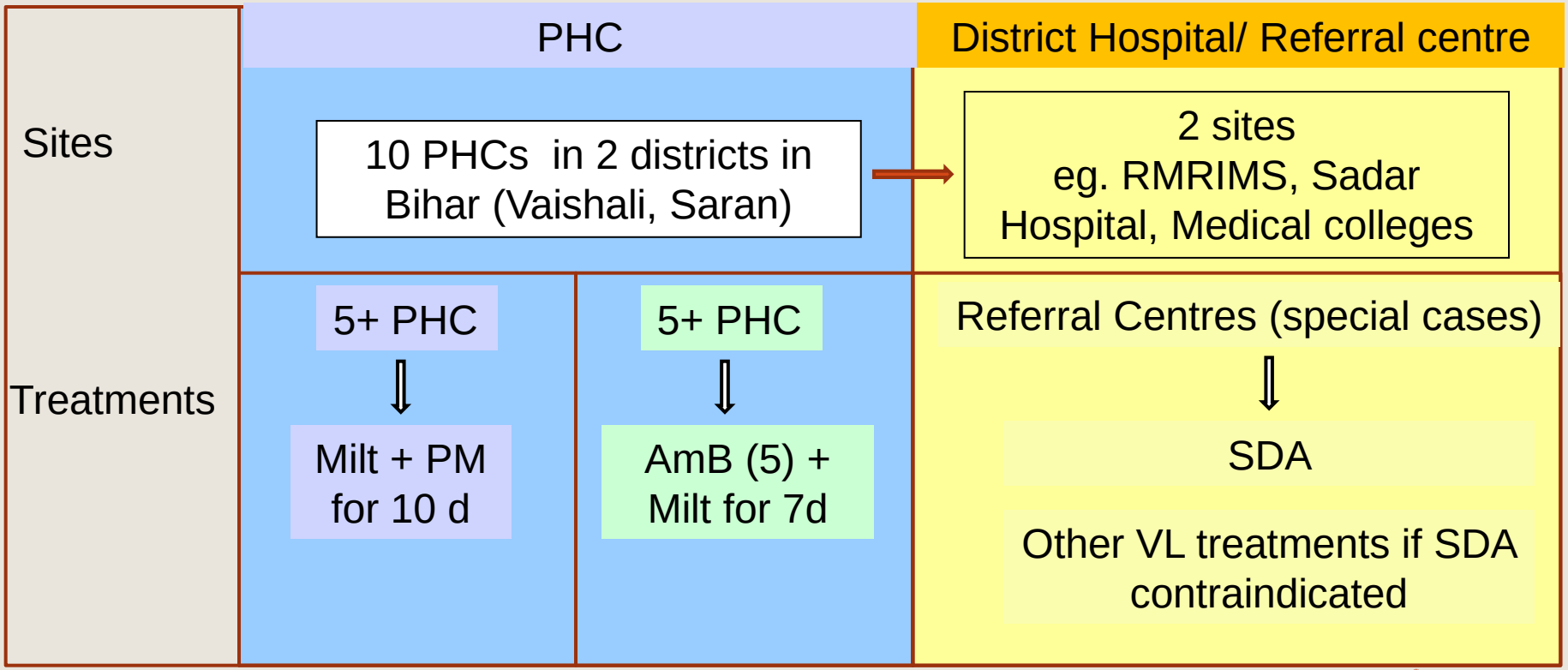
DND*i* Portfolio December 2013



★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL and Chagas Disease) = 1 NCE

Implementation India – effectiveness at different levels of health system

Open label, prospective, non randomised, non comparative, multicentre, observational study to assess the safety and effectiveness of new treatment modalities for VL in public sector



Partners: DNDi, MSF and RMRI

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Implementation India program Step 1 → rolling-out Step 2

- Steering Committee on 10th Dec 2013
  - Data from 919 enrolled patients presented: 626 adults (68%), 293 children (32%)
  - Initial cure (EOT) was > 99% for the 3 treatment arms
  - Cure rates at 6 months follow-up (n= 467/919 subjects) was:
    - Ambisome SD 95%; Amb+Milt 92.6%; Milt+PM 98.3%
  - No new safety signs

- Roll-out Step 2 of the program, including 7 district hospitals and 35 PHCs
  - SDA to be administered at hospital level
  - PM+Milt to be administered at PHC level
  - Target of 2,000 patients treated per arm by Q1 2016, currently 1,532 patients treated

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VL Bangladesh Combination trial

- A Phase III, Open Label, Randomized, Non Inferiority Study
  Milt (2.5mg/Kg/d) + PMC (15mg/Kg/d) for 10 days
  AmB (5mg/kg SD) + Milt (2.5mg/Kg/d) for 8 days
  AmB (5mg/Kg SD) + PMC (15mg/Kg/d) for 11 days, *compared to*
  AmB (15mg/kg total dose in 3 injections)

- 602 patients enrolled in the study
- Final results to be presented to DSMB and the MoH in Sept 2014

Final cure ITT 2 at 6 months follow-up

	Ambisome	AmB+PM	AmB+Milt	PM+Milt
Number of patients	156	159	142	142
Final Cure at 6 month n(%)	155 (98.1)	158 (99.4)	134 (94.4)	139 (97.9)

SSG vs SSG&PM 6 Months FU Results

	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	

WHO TRS 949, 2010

> 3,000 patients treated under PV program – results to be presented in Sept 2014 in LEAP meeting

Melaku *et al.*, *AJTMH* 2007
Musa *et al.*, PLOS NTD 2012

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Safety and efficacy of Ambisome single dose (SD) vs Multiple dose in Eastern Africa

Efficacy at 6 months follow-up by sites

Site	Multiple dose	Single: 7.5 mg/kg	Single: 10 mg/kg
Gondar	10/14 (71%, 42-92%)	1/9 (11%, <1-48%)	**3/9 (33%, 7-70%)**
Arba Minch	23/23 (100%, 83-100%)	7/11 (64%, 31-89%)	**13/13 (100%, 75-100%)**
Kassab	13/17 (76%, 50-93%)	-*	**7/18 (39%, 17-64%)**
Overall	**46/54 (85%, 73-93%)**	**8/20 (40%, 19-64%)**	**23/40 (58%, 41-73%)**

Definitive cure by centre, ITT complete-case analysis
Data are number of patients with definitive cure / number of patients randomised
(%: exact binomial 95% CI)

The trial was terminated because of low efficacy of both regimens

Khalil *et al.*, PLOS NTD 2014

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LEAP 0208 – Alternative combination therapy in Eastern Africa

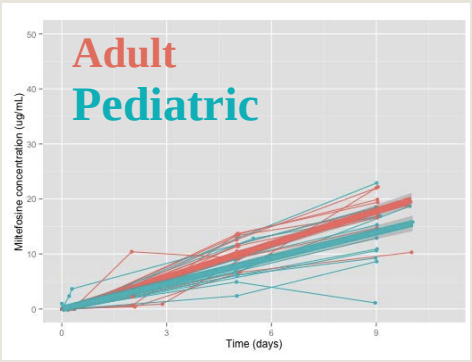
AmB+SSG	Amb 10mg/Kg SD + SSG 20mg/Kg/d, 10d
AmB+Milt	Amb 10mg/Kg SD + miltefosine 2.5 mg/Kg/d, 10d
Miltefosine	Miltefosine 2.5mg/Kg/d for 28d

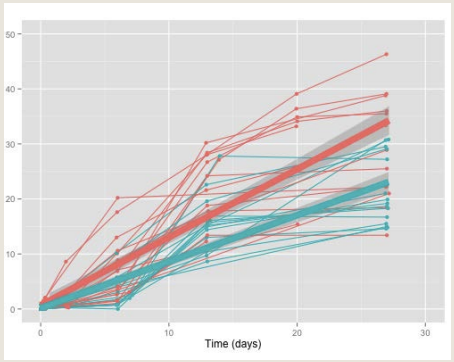
	AmBisome® + SSG	AmBisome® + Miltefosine	Miltefosine
Proportion cured (p_{28}, Day 28)	0.85	0.85	0.85
Number of patients with non-missing cure status at both days 28 and 210 (N_{28})	51	49	51
Number cured at day 28	47	46	45
of whom still cured at			
as a prop			
Number not cured at day 28			
of whom became cured at			
as a proportion (s)	0.25	0.33	0.17
Proportion cured at day 210 (p_{210})	0.87	0.77	0.72
Standard error of p_{210}	0.052	0.067	0.063
95% confidence interval for p_{210}	0.77-0.97	0.64-0.90	0.60-0.85

None of the combination regimens reached > 90% efficacy at 6mo to move to Phase III development

Miltefosine PK and clinical outcome

Miltefosine concentration over time

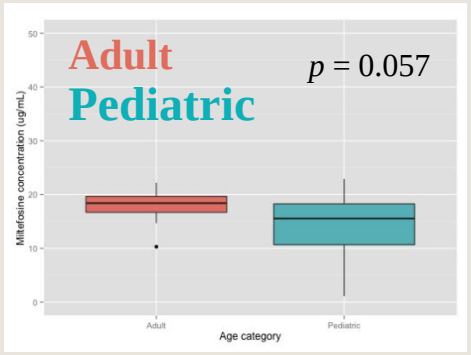


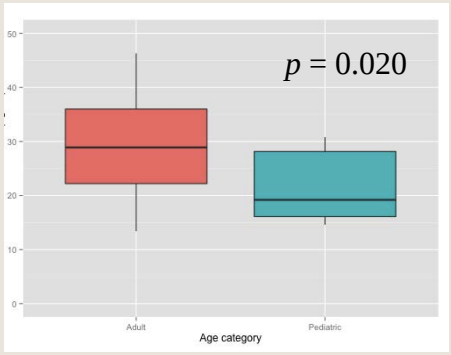


Ambisome + Miltefosine

Miltefosine alone

Miltefosine concentration at end of treatment





Ambisome + Miltefosine

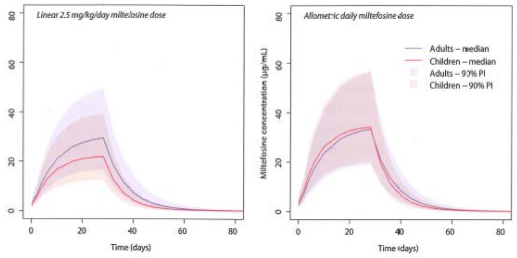
Miltefosine alone

D210 Efficacy by age group

	AmBisome® + Miltefosine	Miltefosine monotherapy
Final number of patients		
7-12	27	22
13-60	22	29
Final number cured, n (%)		
7-12	20 (74.1%)	13 (59.1%)
13-60	20 (90%)	25 (86.2%)
Fisher's exact test p-value	*0.25*	*0.061*

Children had poorer clinical response as compared to adults, which can be explained by the underexposure to the drug.

Allometric dose to be assessed in children



Study was not powered for sub-group analysis.

Fexinidazole PoC trial in Sudan

Primary Objective

- to evaluate the efficacy of fexinidazole in primary VL patients

Secondary Objectives

To assess the:

- safety profile of fexinidazole in primary VL patients
- pharmacokinetic and pharmacodynamic profile of fexinidazole in primary VL patients

Implementation of Fexi trial in Sudan

Current status:

- 167 suspected cases of VL
- 99 confirmed VL diagnosis (59%)
- 14 fulfilled criteria (14/99= 14%)
- Exclusion due to age, malnutrition, labs, Hep B/C, HIV, lactation, no consent

Strategies to boost recruitment:

- Awareness and active case search through health workers
- Referrals network
- Assessment to open a new site in highly endemic area, Um el kher - ~ 1,000 VL cases treated in 2013

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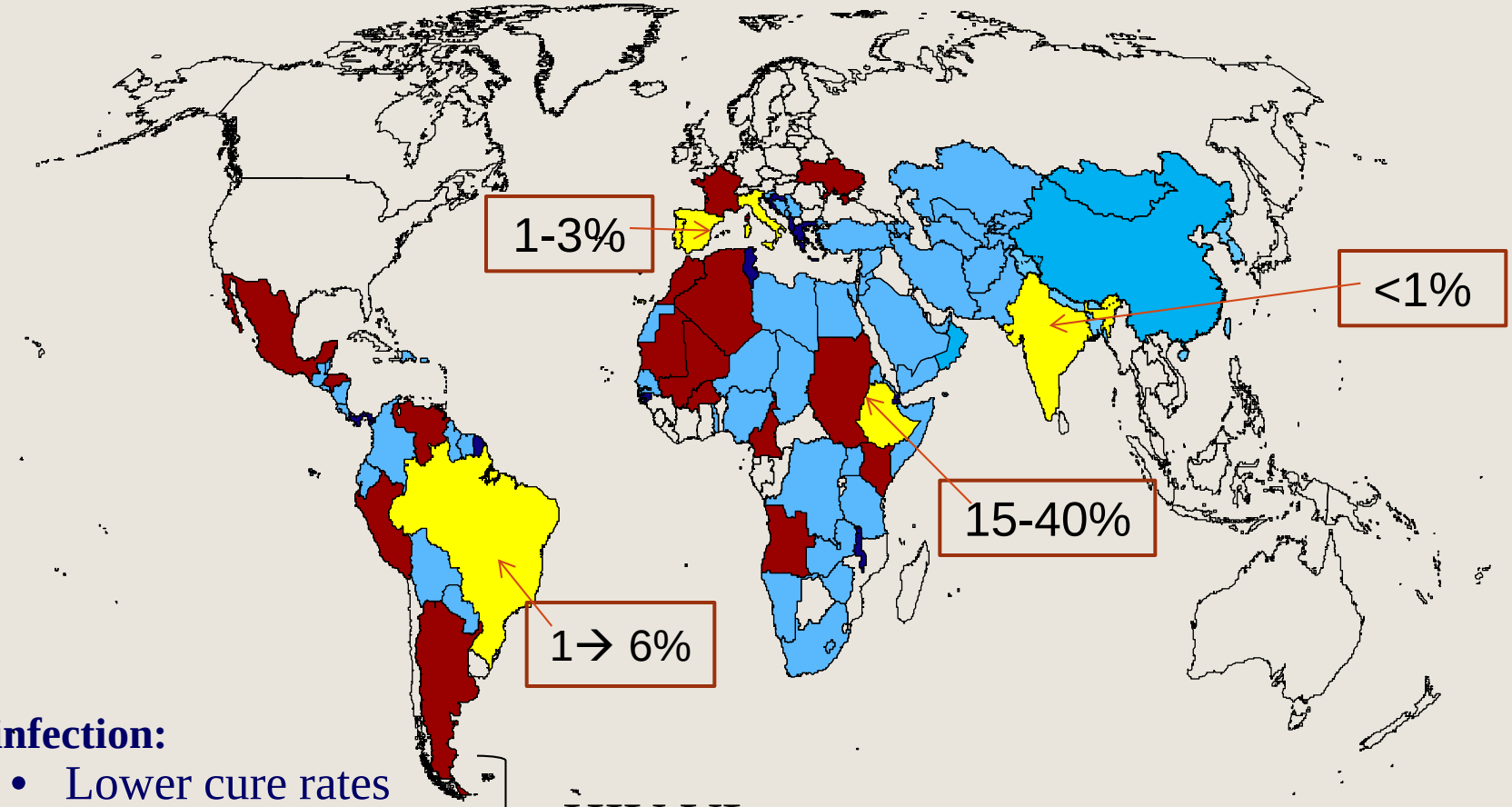
HIV & *Leishmania* co-infection



Co-infection:

- Lower cure rates
- Higher drug toxicity
- Higher relapse rates
- Higher mortality rates

HIV-VL study in Ethiopia

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HIV-VL 0511 study in Ethiopia

A randomized, parallel arm, open-label clinical trial to assess the safety and efficacy of the combination of AmBisome® plus miltefosine and AmBisome® alone for the treatment of VL in HIV co-infected patients in Ethiopia

- **Primary Objective:**

To assess the efficacy of a combination regimen of AmBisome® + miltefosine and AmBisome® monotherapy in Ethiopian co-infected HIV + VL patients.

- **Secondary Objectives:**

1. To evaluate relapse-free survival at day 390 (after initial cure at day 29 or cure at day 58 after extended treatment).

2. To assess safety of the regimens.

3. To evaluate of viral load and CD4 count in all patients

4. To evaluate the PK of ARV, Ambisome and miltefosine and immune function markers in a subset of patients

Treatment Arms:

Ambisome, 5mg/Kg/d, D1-5, D10, D17, D24 → total dose 40mg/Kg

Amb 5mg/Kg/d in 6 alternative days (30mg/Kg) + Milt 2.5mg/Kg/d, 28 days

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VL in Latin America – 'LV BRASIL' trial

- MoH Sponsored trial, LVBRASIL, started Feb 2011
- 5 active sites: Aracaju, Belo Horizonte, Fortaleza, Montes Claros and Teresina
- 4 study arms: currently recommended Rx and combo Amb+Glucantime → to asssess superiority of alternative Rx as compared to 1st line Glucantime
- Interim safety analysis in Q3 2012 → due to higher toxicity, Ampho B deoxycholate arm was dropped
- Planned interim analysis (50% recruitment) to assess safety and efficacy: none of the treatment regimens had > 90% cure rate.
- 380/426 patients recruited → patients under follow-up until Q4 2014
- Final report by Q1 2015 to inform Brazilian National Control Program

National Control Program revised guidelines in Oct 2013:
Glucantime remains as 1st line therapy, Ambisome defined as 2nd line, and AmpB deoxycholate shifted to 3rd line therapy.

Thank you!

Africa, LEAP Platform: KEMRI, University of Addis Ababa, Institute of Endemic Diseases, Gondar University, Makarere University; Médecins Sans Frontières; National control programs of Ethiopia, Kenya, Uganda and Sudan.

Asia: India- RMRI, MSF, NVBDCP, Bihar State Health Society; Bangladesh- SHSMCH, ICDDR,B

Latin America (LA): Universidade de Brasília (UnB), Centro de Pesquisa René Rachou / FIOCRUZ MG (CPqRR), Universidade Federal do Piauí (UFP), Hospital Infantil João Paulo II, Universidade Estadual de Montes Claros (Unimontes), Universidade Federal de Sergipe (UFS) and Hospital São José de Doenças Infecciosas; Brazilian MoH, national control program.

LSHTM, Utrecht University, MSF, ITM Antwerp, FIND, I+ solutions, KIT, SGS, Cardiabase, GVK BIO

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