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Pitfalls in the treatment of visceral leishmaniasis

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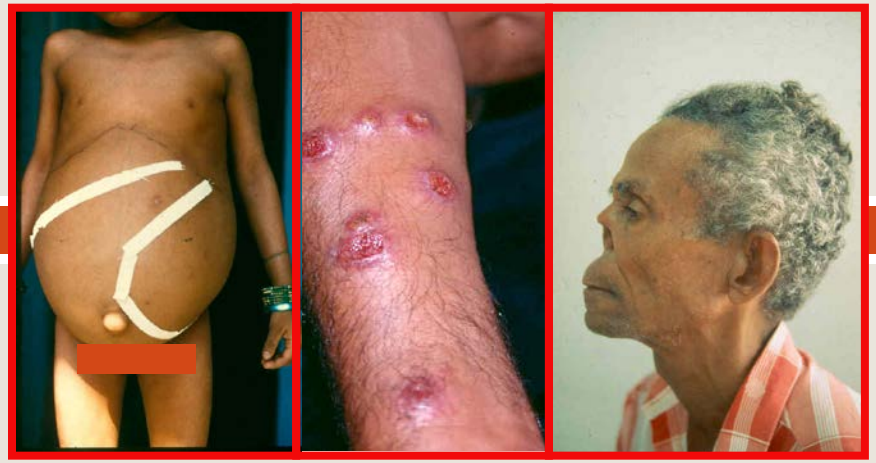
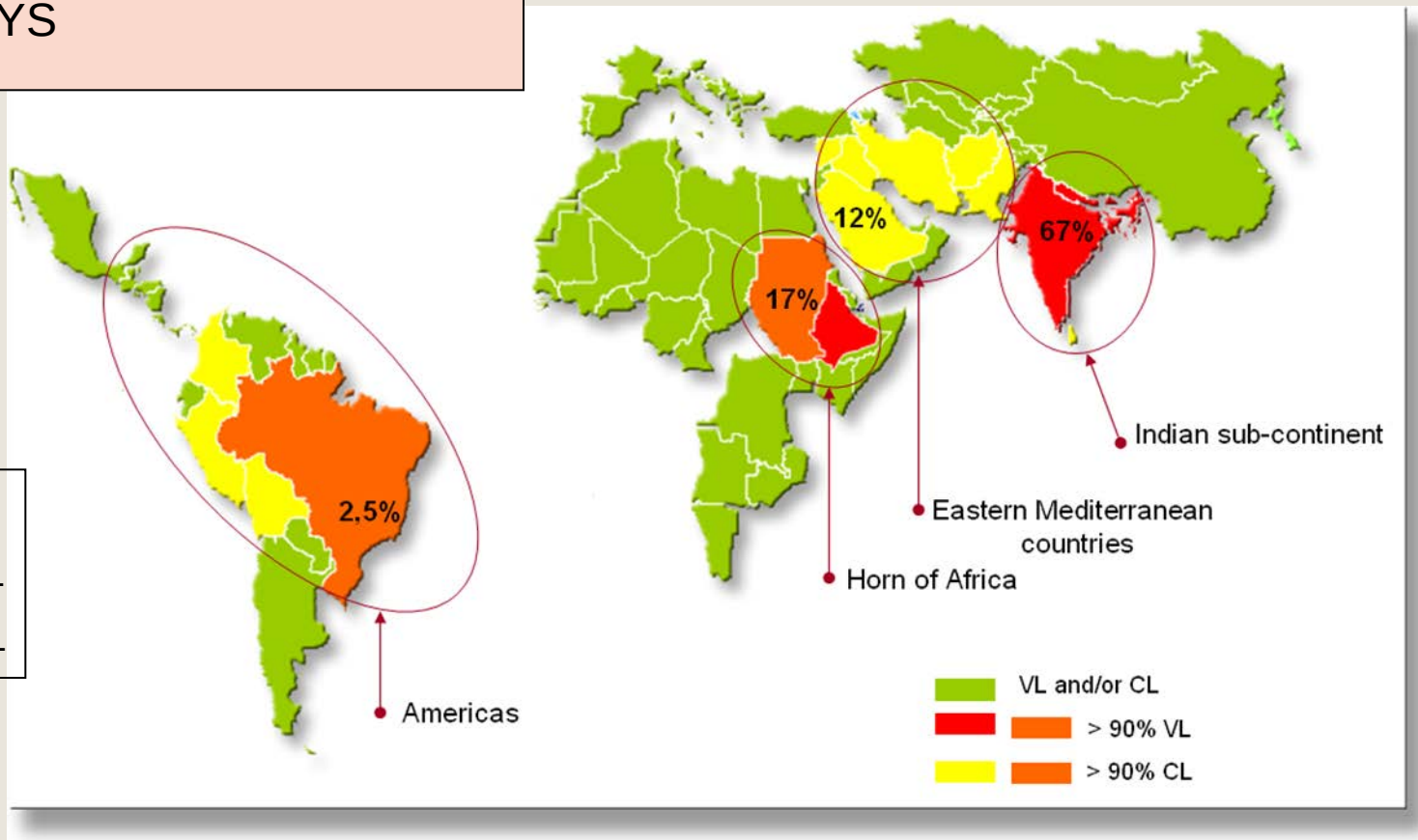
Leishmaniasis



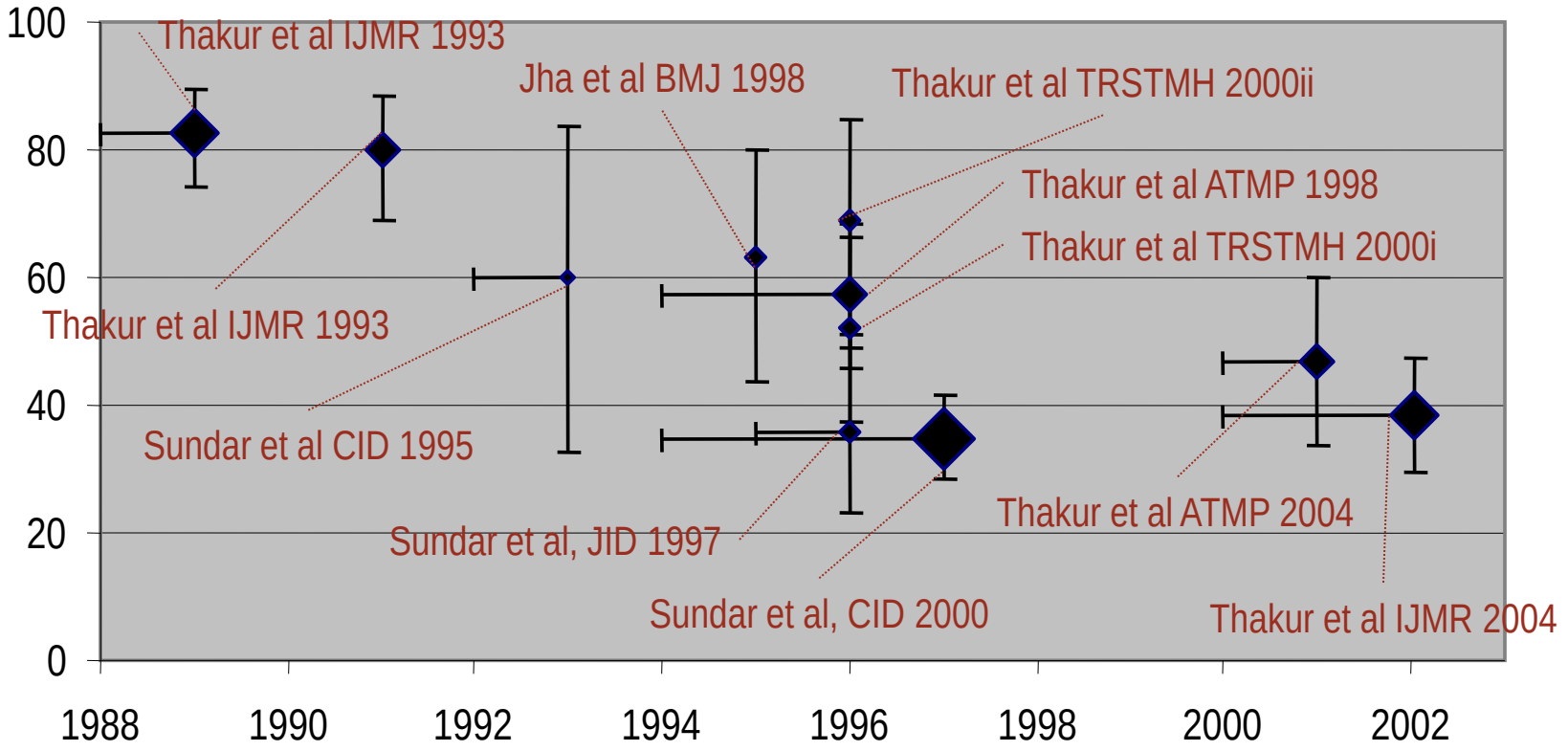
- VL & CL (MCL, DCL, PKDL, LR, HIV/VL)
- 98 endemic countries
- Incidence: 0,4 M VL, 1,2 M CL cases/yr
- 2,35 million DALYS



VL and/or CL
> 90% VL
> 90% CL

Efficacy of SSG 20mg/kg/d at 6-month follow-up in Bihar, India during 1988-2002.

mean, 95%CI; bar on the X axis is duration of study;
marker size proportional to study size



Alvar, Croft & Olliaro. Advances in Parasitology Vol61: 224-261 (2006)
Olliaro et al, Lancet Infect Dis. 2005 Dec;5(12):763-74

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Limitations of VL drugs

Pentavalent antimonials	High toxicity: pancreatitis, hepatitis and cardiotoxicity (arrhythmias) 30 day IV/IM treatment in hospital painful injections
Amphotericin B	Needs slow IV infusion; infusion reactions (fever); nephrotoxic; needs lab monitoring
Liposomal amphotericin B	Expensive requires slow IV infusion over 1-2 hours however long term hospitalization is not required
Miltefosine	The only oral treatment for VL teratogenic expensive GI toxicity, hepato- & renal toxicity
Paromomycin	an aminoglycoside, therefore nephro- and ototoxicity possible: although reversible high tone audiometric shift may occasionally occur during treatment geographical variation in response

Monotherapy *versus*

Combination of drugs:

- response optimization with shorter duration, better compliance to Rx, reduced costs
- improved safety profile
- resistance prevention, expanding drug life

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New evidence to guide policy change – which one to choose?

Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial

Shyam Sundar, Prabhat Kumar Sinha, Madhukar Rai, Deepak Kumar Verma, Kumar Nawin, Shanawwaj Alam, Jaya Chakravarty, Michel Vaillant, Neena Verma, Krishna Pandey, Poonam Kumari, Chandra Shekhar Lal, Rakesh Arora, Bhawna Sharma, Sally Ellis, Nathalie Strub-Wourgaft, Manica Balasegaram, Piero Olliaro, Pradeep Das, Farrokh Modabber

www.thelancet.com **Published online January 20, 2011** **DOI:10.1016/S0140-6736(10)62050-8**

	Amphotericin B	Liposomal amphotericin B+ miltefosine	Liposomal amphotericin B+ paromomycin	Miltefosine+ paromomycin
Intention-to-treat population				
Number of patients (634)	157	160	158	159
Number of patients cured (%, 95% CI)	146 (93·0, 87·5–96·3)	156 (97·5, 93·3–99·2)	154 (97·5, 93·2–99·2)	157 (98·7, 95·1–99·8)
Per-protocol population				
Number of patients (618)	148	157	155	158
Number of patients cured (%, 95% CI)	146 (98·6, 94·7–99·8)	155 (98·7, 95·0–99·8)	153 (98·7, 94·9–99·8)	156 (98·7, 95·0–99·8)

Table 2: **Definitive cure at 6 months, by treatment group**

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New evidence to guide policy change – which one to choose?

Single-Dose Liposomal Amphotericin B for Visceral Leishmaniasis in India

Shyam Sundar, M.D., Jaya Chakravarty, M.D., Dipti Agarwal, M.D., Madhukar Rai, M.D., and Henry W. Murray, M.D.

N Engl J Med 2010;362:504-12.

Table 2. Response to Treatment.

Variable	Liposomal Amphotericin B (N=304)	Amphotericin B Deoxycholate (N=108)
Removed from study — no.	0	2
Completed treatment — no.	304	106
Apparent cure at day 30 — no.	304	106
Relapse — no. (%)*	13 (4.3)	2 (1.9)
Lost to follow-up — no.	0	0
Definitive cure at 6 mo†		
Intention-to-treat population		
No. of patients	291	104
Percent (95% CI)	95.7 (93.4–97.9)	96.3 (92.6–99.9)
Per-protocol population‡		
No. of patients	291	104
Percent (95% CI)	95.7 (93.4–97.9)	98.1 (95.5–100.0)

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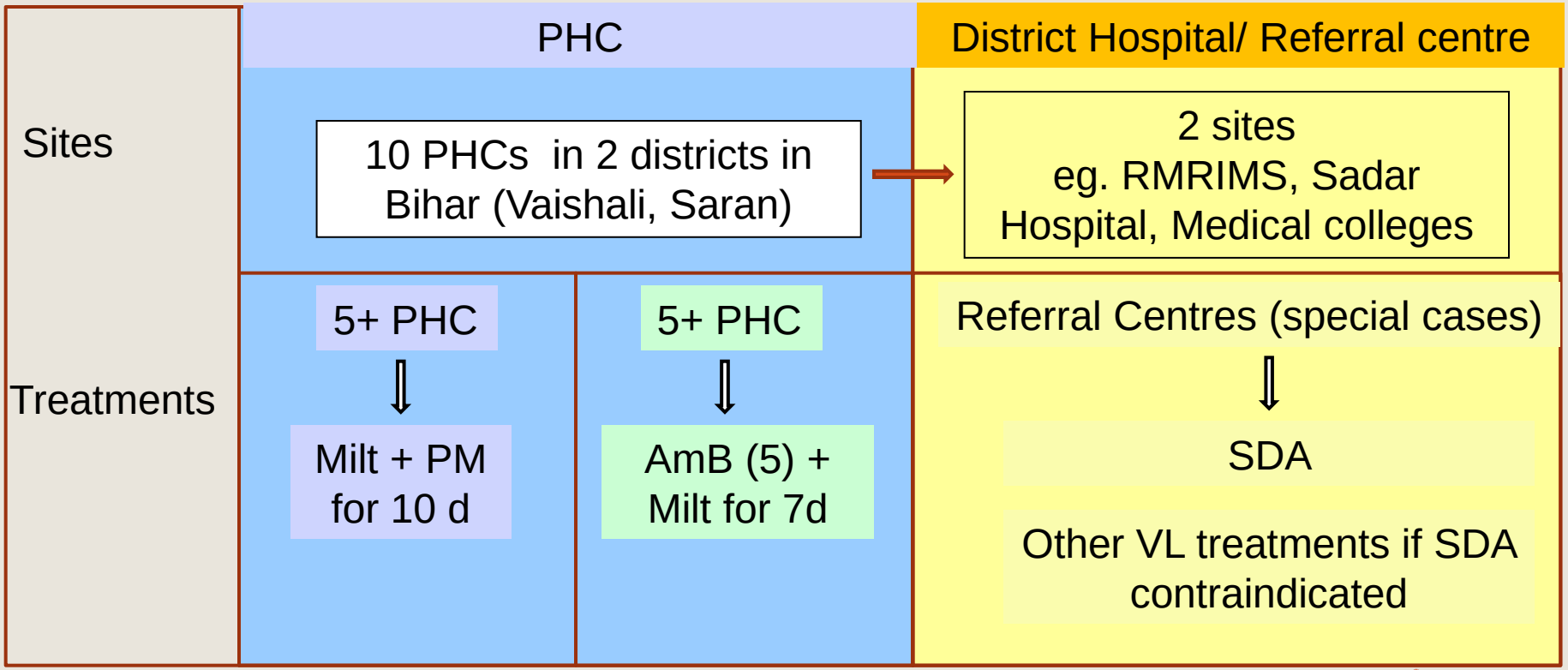
Implementation India – effectiveness at different levels of health system

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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Liposomal amphotericin B single dose (10mg/kg) at PHC level in Bangladesh (Mondal et al., Lancet GH, 2014)

	Intention-to-treat analysis		Per-protocol analysis*	
	n/N (%)	Difference (95% CI; p value)	n/N (%)	Difference (95% CI; p value)
Initial cure				
By age group		9·3% (1·2–17·3; 0·075)		8·6%(1·0–16·5; 0·041)
Children	159/175 (91%)		159/174 (91%)	
Adult	102†/125 (82%)		101/122 (83%)	
By visceral leishmaniasis type		9·2% (2·0–16·5; 0·075)		8·0% (1·0–15·2; 0·121)
Primary	197†/232 (85%)		197/229 (86%)	
Relapse	64/68 (94%)		63/67 (94%)	
Overall	261†/300 (87%)		260/296 (88%)	
Final cure				
By age group		1·6% (–2·4–5·6; 0·664)		2·6% (–1·5–5·7; 0·282)
Children	168/175 (96%)		168/174 (97%)	
Adult	122†/125 (98%)		121/122 (99%)	
By visceral leishmaniasis type		4·3% (1·7–6·9; 0·175)		3·1% (1·0–5·3; 0·322)
Primary	222†/232 (96%)		222/229 (97%)	
Relapse	68/68 (100%)		67/67 (100%)	
Overall	290†/300 (97%)		289/296 (98%)	

*Four patients were excluded; one patient was lost to follow-up because of a serious adverse events not regarded as related to study drug; one patient had a partial treatment; one patient was misdiagnosed; and one patient was hypersensitive to amphotericin B. †One patient with partial treatment achieved initial and final cure.

Table 2: **Efficacy of single-dose liposomal amphotericin B for visceral leishmaniasis**

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)

Many relapses occurred > 6 months after the end of treatment

AMBISOME in INDIA

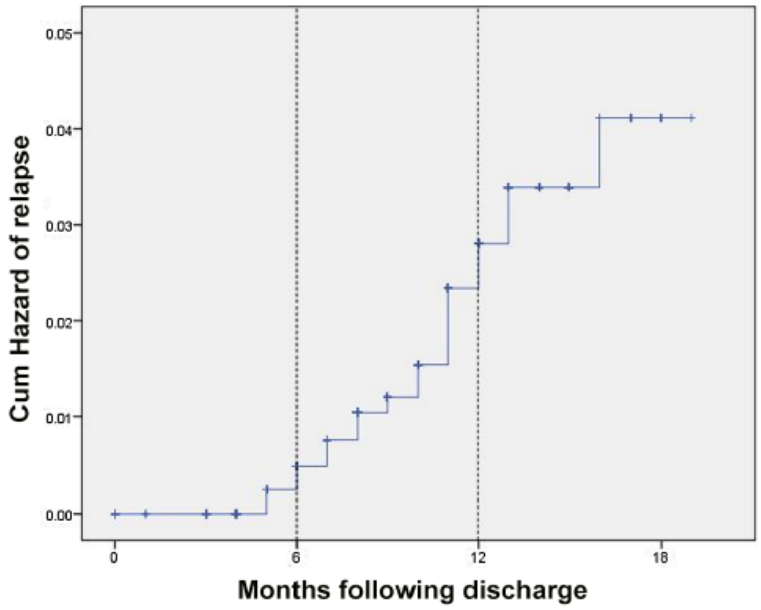

Figure 3. Censored Kaplan Meier curve showing the cumulative hazard of relapse over the time after discharge.
doi:10.1371/journal.pntd.0002603.g003

- **Amb 4 x 5mg/Kg regimen**
- **0.3% and 3.2% failure at 6 & 12m**
- **Mean 9.6 m to relapse**
- **70% between 6 and 12m**

(Burza et al., 2014)

MILTEFOSINE in NEPAL

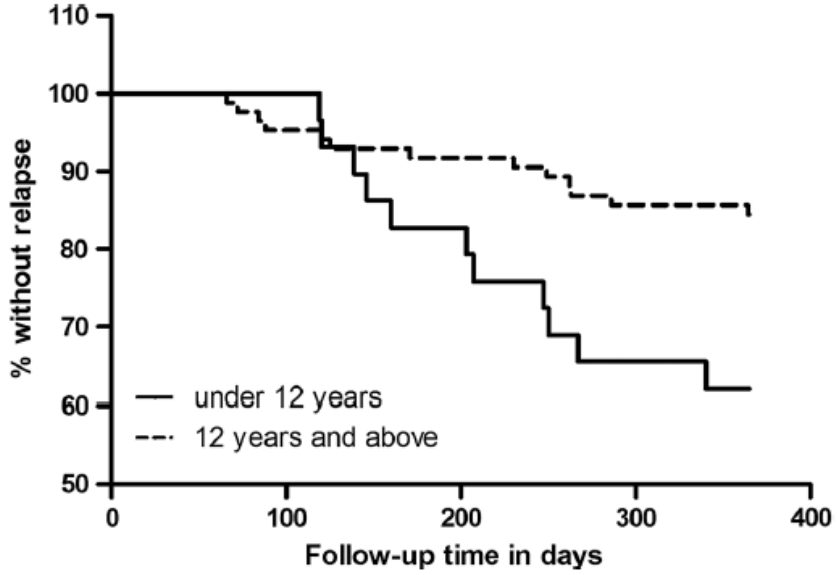

Figure 2. Kaplan-Meier plot for the 2 age groups, time without relapse.

- **10.8% and 20% failure at 6 & 12m**
- **50% of relapses after 6m**
- **Survival analysis by age consistent with PK data**

(Rijal et al., 2013)

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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

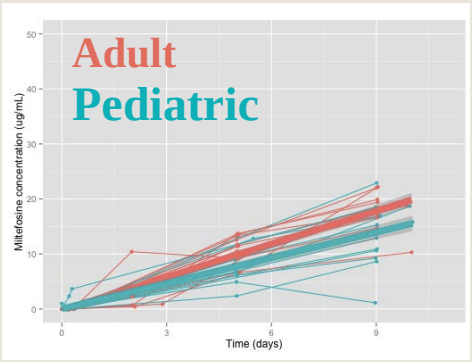
AmB+SSG	Amb 10mg/Kg SD + SSG 20mg/Kg/d, 10d
AmB+Milt	Amb 10mg/Kg SD + miltefosine 2.5 mg/Kg/d, 10d
Miltefosine	Miltefosine 2.5mg/Kg/d for 28d

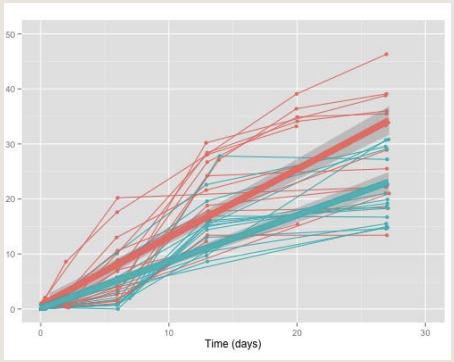
	AmBisome® + SSG	AmBisome® + Miltefosine	Miltefosine
Proportion cured (p_{28}, Day 28)	0.85	0.85	0.85
Number of patients with non-missing cure status at both days 28 and 210 (N_{28})	51	49	51
Number cured at day 28	47	46	45
of whom still cured at			
as a prop			
Number not cured at day 28			
of whom became 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

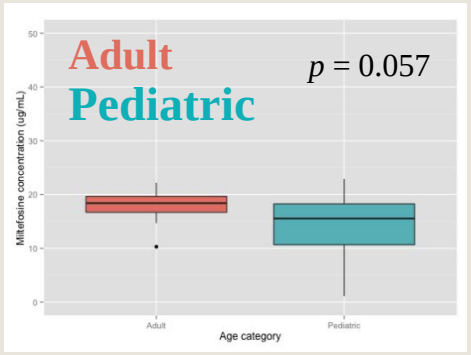


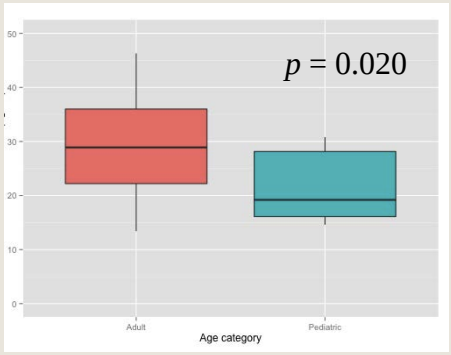


Ambisome + Miltefosine

Miltefosine alone

Miltefosine concentration at end of treatment





Ambisome + Miltefosine

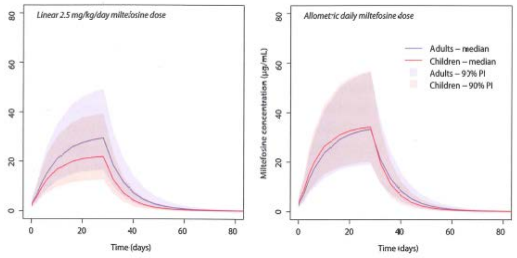
Miltefosine alone

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.

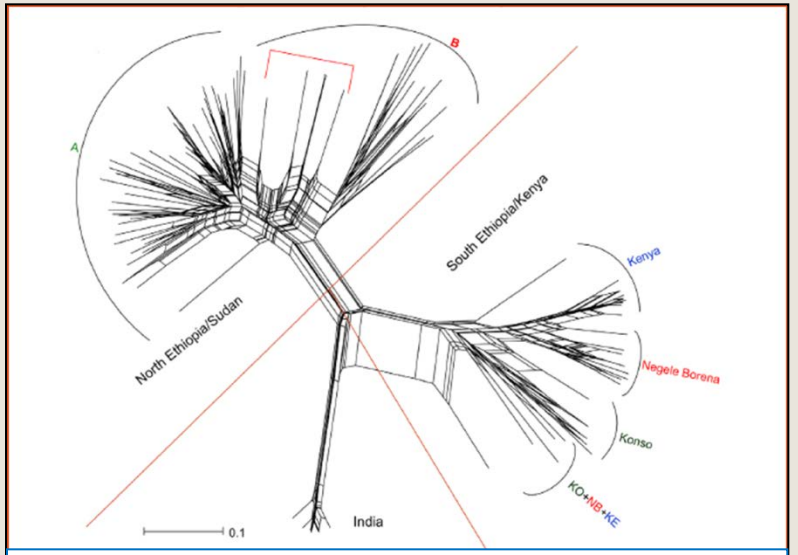
Pitfalls in chemotherapy: the African case

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)

Table 2. Cure (efficacy) at end of treatment and at 6 months after treatment.

	SSG	PM	P*†
• Um el Kher, Sudan	14/17 (82.4%)	4/28 (14.3%)	<0.001
• Kassab, Sudan	14/15 (93.3%)	7/15 (46.7%)	0.014
• Kenya	15/15 (100.0%)	12/15 (80.0%)	0.224
• Gondar, Ethiopia	37/40 (92.5%)	30/40 (75.0%)	0.066
• Arba Minch, Ethiopia	27/29 (93.1%)	28/29 (96.6%)	1.000
P*‡	0.568	<0.001	

Hailu PLoS NTD 2010



Gelanew PLoS NTD 2010

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.

R&D Challenges on VL

- Identification of oral NCEs, to be used in combination that are efficacious and safe to be used in the field
- Need to develop strategies that respond to patients needs adapted to regional contexts with variable responses
- Clinical development plans for any new regimen need to include paediatric populations and the need to develop age suitable formulations
- Other challenges: HIV-VL, PKDL patients, and asymptomatic carriers
- Resistance monitoring surveillance

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Thank you!

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