Challenges in the treatment of Kala-azar in the Indian sub-continent

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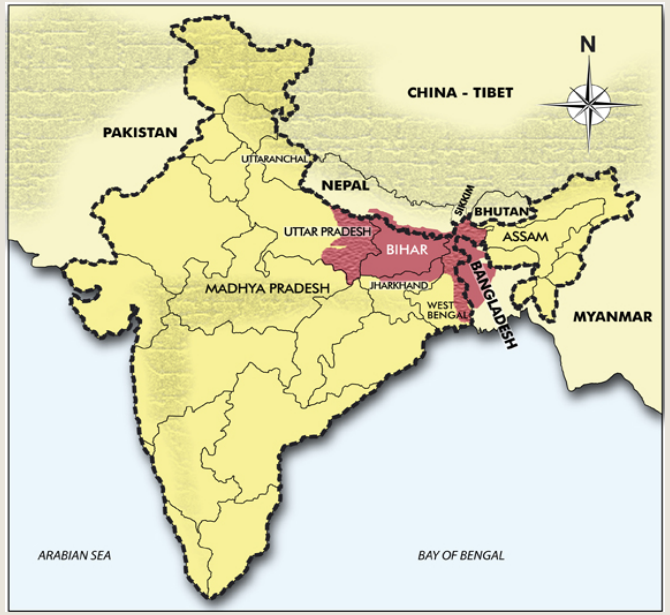
Kala-azar reported cases (average 2004-08) and estimates



	Cases reported/year	Estimated annual cases
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**

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Challenges in the treatment in kala-azar

- Access to care
- Efficacy and tolerability of current anti VL treatment
- Cost of anti VL treatment
- Emergence of parasite drug resistance
- Others: HIV-VL co-infections

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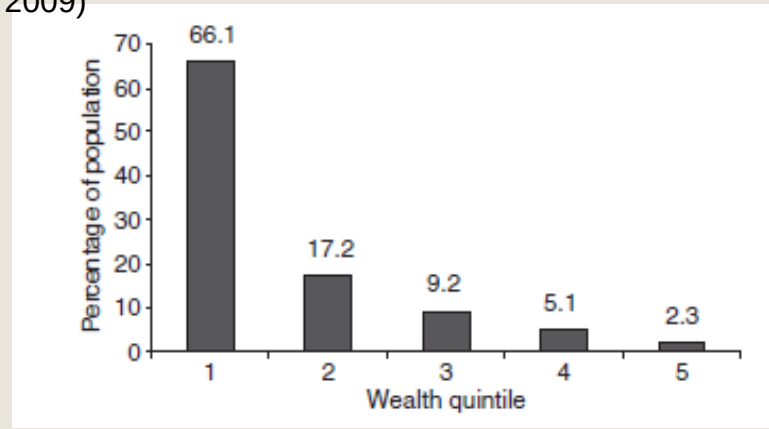
Kala-azar: access to clinical care

PCA of asset index (Boelaert, 2009)



83% HH from the 2 lowest quintiles

Women high CFR in Bangladesh (Ahluwalia, 2003)

- CFR 19% among adult women, compared with 6-8% among other demographic groups
- Female patients were ill longer than males before they received treatment

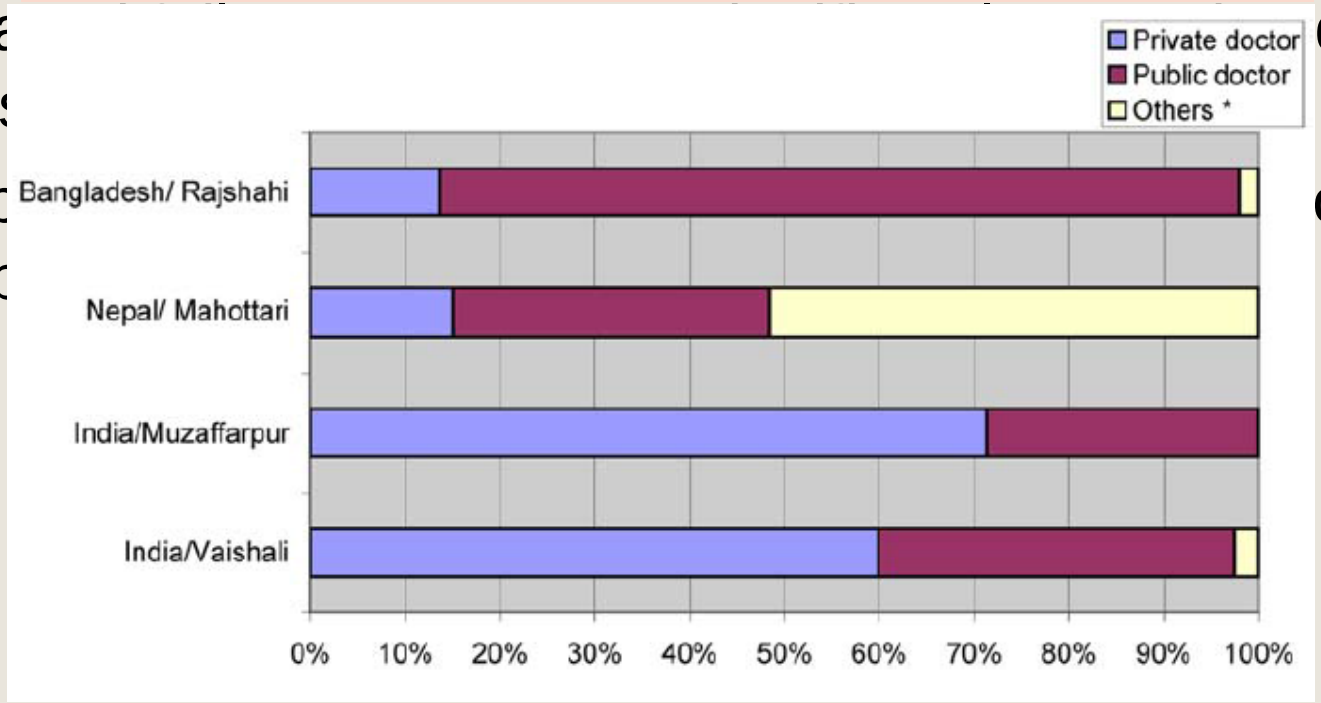
High VL CFR in tribal populations in Bangladesh (Huda, 2014)

- 51 094 population from Godagari (16% tribals) and Trishal upazilla: screened for VL deaths
- Mean VL CFR 6.12% (12/196); 75% (9/12) occurred at home
- CFR in the tribal ethnic 17 times higher. OR 18 (95% CI 3.6, 90.6)

Delay in treatment and outcome in kala-azar

- Anaemia, severe malnutrition and long duration of illness: increased risk for mortal
- Increa d with fever for ≥12 week
- Low p or ease of access or time p

Choice of health care provider *(Mondal et al 2009)*



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Currently available drugs

AmBisome

Amphotericin B

miltefosine

Antimonials

Paromomycin

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Currently available treatments for kala-azar

Limitations of current treatment:

- costly
- poorly tolerated
- difficult to administer
- long dosing/treatment
- not adapted to high temperatures

What is needed:

- simple oral combination therapy
  - maintain or improve efficacy
  - prevent or delay emergence of resistance
  - reduce treatment duration and cost
  - pan-geographic use
  - could be used for PKDL, HIV-VL, asymptomatic carriers

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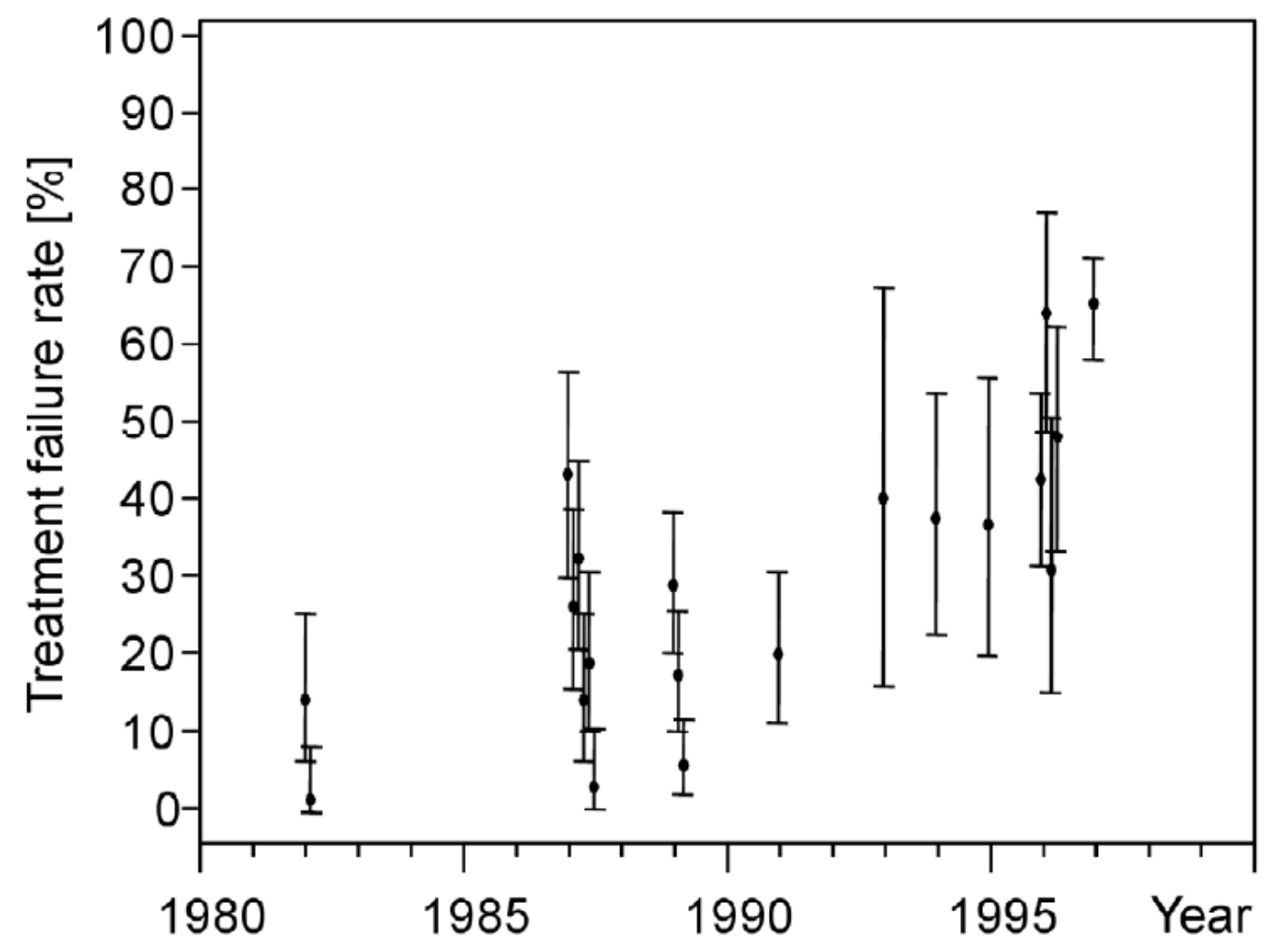
Pentavalent antimonials failure rates 1980 -1997



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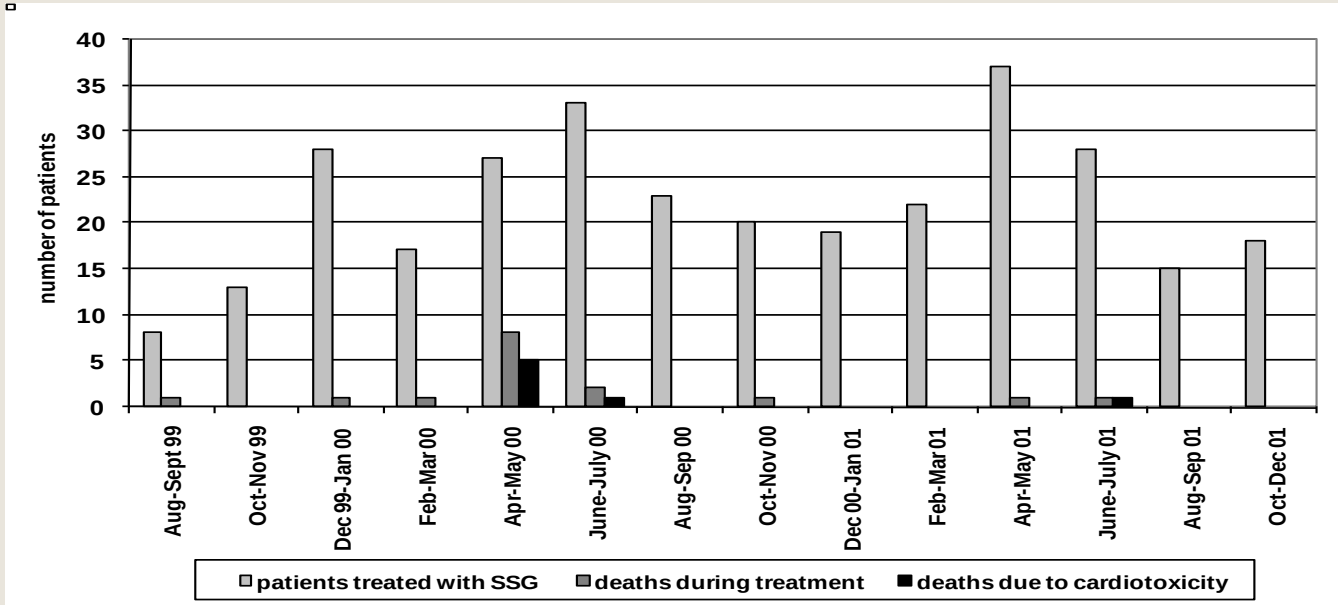
Toxicity of antimonials



Deaths due to cardiotoxicity
33% (8/23) deaths with the new batch died (Rijal 2003)

SEVERE CARDIOTOXICITY: 3/8 deaths
HIGH-OSMOLARITY LOT OF SSG (Sundar 1998)

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Miltefosine

- Only oral drug for kala-azar
- 28 days regimen: compliance a challenge
- Potentially teratogenic: contraception for 4 months in women of child bearing age group
- Common adverse events
  - Vomiting: 38%; Diarrhoea: 20%
  - ↑ Transaminase: 15%; Renal dysfunction: 10%
  - 2% severe adverse event (phase 4 trial India) *(Bhattacharya 2007)*

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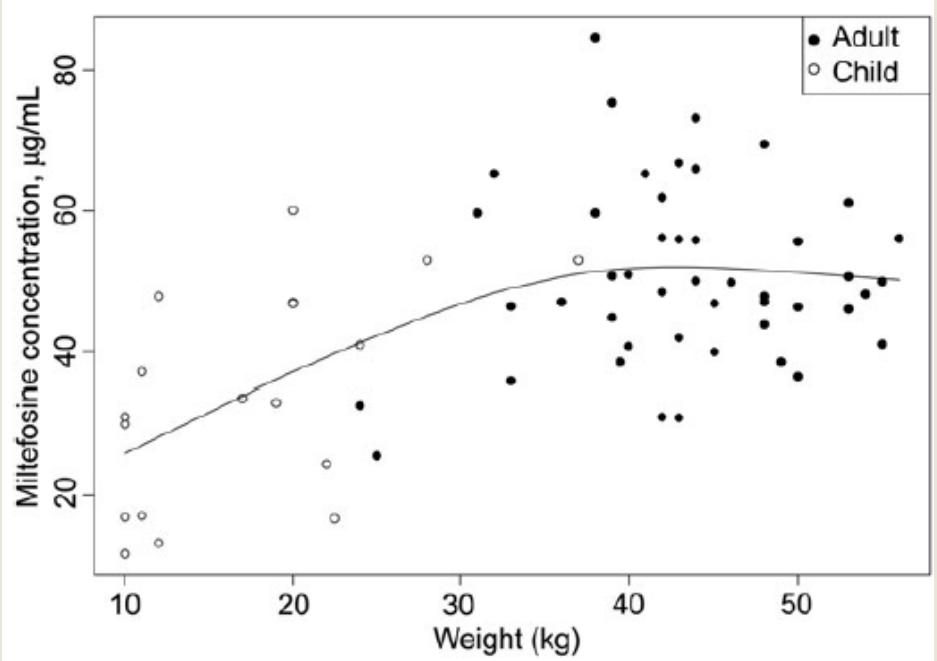
Miltefosine: increasing treatment failure

- 85% Cure rate in per protocol analysis. *Rahman, 2011*
- Relapse in up to one-fifth of the MIL-treated patients observed. *Sundar, 2012; Rijal, 2013.*
- Treatment failure not associated with re-infection, compliance, drug resistance. Age< 12 = risk factor for failure *Rijal 2013*
- Achieving a sufficient exposure to miltefosine is a significant and critical factor for VL treatment success. *Dorlo 2014*
- Not (yet) *MIL-resistance in natural populations; isolates with higher* tolerance in PKDL-treated patients (2 rounds of treatment). *Bhandari, 2012*



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Liposomal amphotericin B: Ambisome

- Shorter treatment, low toxicity.
- Cost US $ 200/ vial; requires cool chain (2 to 25 C)
- December 2011, Gilead to donate 445,000 vials of AmBisome over five years
- Single dose Ambisome (10 mg/kg): Cure rate
  - Phase III: 95.7% (95% CI 93.4;97.9) *Sundar 2010*
  - Feasibility study sub-district hospitals Bangladesh: 97% cure rates. *Mondal 2014*
- Currently 1st line treatment in Bangladesh, India and Nepal.

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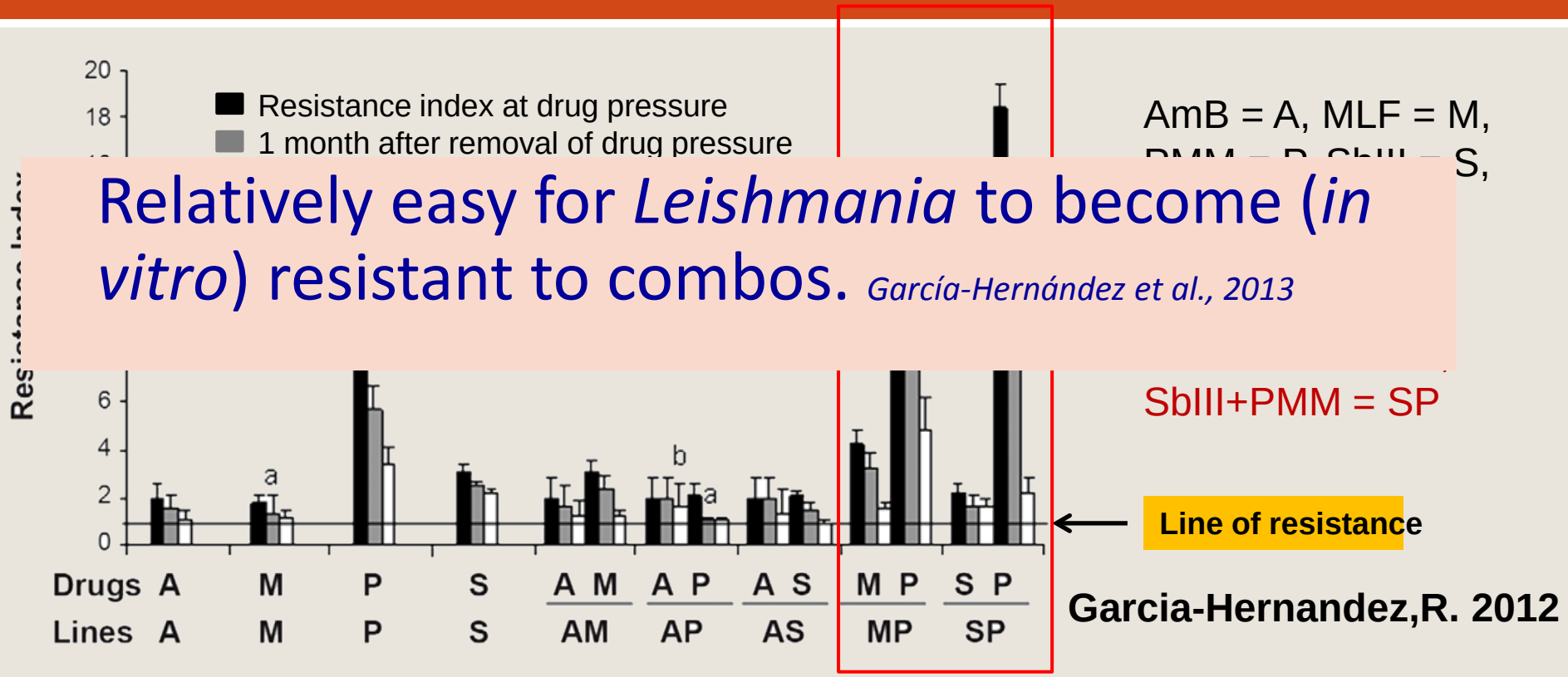
Combination regimens

Multidrug treatment with standard therapy for VL in India Non inferiority Phase III. Sundar 2010				
Regimens (no. of pt.)	Ampho B (157)	AmB+PM (158)	AmB+Milt (160)	PM+Milt (159)
Cure 6 month % (95% CI)	93 (87.5-96.3)	97.5 (93.2-99.2)	97.5 (93.3-99.2)	98.7 (95.1-99.8)

A Phase III, Open Label, Randomized, Non Inferiority Study in Bangladesh, 2014.				
Number of patients	Ambisome 156	AmB+PM 159	AmB+Milt 142	PM+Milt 142
Cure at 6 month n(%)	155 (98.1)	158 (99.4)	134 (94.4)	139 (97.9)

Safety and Effectiveness of new treatment modalities at field level in India (2011-14)			
Number of patients	Ambisome 506	AmB+Milt 294	PM+Milt 302
Final Cure at 6 month (%)	94.7	90.1	97.4

L . Donovani resistance to drugs



Relatively easy for *Leishmania* to become (*in vitro*) resistant to combos. *García-Hernández et al., 2013*

AmB = A, MLF = M,

SbIII+PMM = SP

Line of resistance

Garcia-Hernandez,R. 2012

- Resistance to the combinations miltefosine/paromomycin and SbIII/paromomycin is easily inducible.
- The outcomes have been validated in intracellular amastigotes.
- Long-term efficacy of drug combinations with paromomycin?

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HIV-VL co-infection and outcome

- Screening 2077 VL patients (≥14 years) for HIV: 5.6% HIV +ve *(Burza 2014)*
- Estimated mortality risk:
  - 6 months: 14.3%
  - 12 months: 22.4%
  - 24 months: 29.7%
- Estimated risk of relapse:
  - 1 year: 16.1%
  - 2 years: 20.4%
  - 4 years: 25.9%
- ART treatment: 64–66% reduced risk of mortality and 75% reduced risk of relapse

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Conclusions

- Access to care related to socio-economic class remains a challenge. Active case finding strategies would help.
- Treatment failure to current drugs trend to increase over time. Limited no. of treatments available at present.
- Resistance to drugs demonstrated. Monotherapy of miltefosine and paromomycin recommended to be stopped and replaced by SAB or combinations.
- **Recommendation to programme: Monitoring !**

- Treatment effectiveness e.g cohort event monitoring
- Drug resistance (also for drug-combinations)
- Drug quality, dosage, access …
- HIV co-infections

THANK YOU

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