Effectiveness and safety profile of new treatments for Kala-azar at public health facilities in Bihar, India

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ECTMIH, 8 Sep 2015, Basel

Introduction

New treatment regimens developed only in the last few years from already existing drugs for VL, specifically - AmBisome®, paromomycin and miltefosine

These new treatment modalities have now been recommended by WHO Expert Committee on the control of leishmaniasis (March 2010) and RTAG (WHO SEARO)

There was need to generate data to make evidence-based recommendations for replacing Miltefosine monotherapy with ambisome and combination therapies in the National kala-azar Elimination Program

Rationale:
Reducing the duration of therapy will improve compliance, reduce side effects and also prevent the emergence of resistant parasites and thus increase the duration of effectiveness of available drugs.

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Project Implementation Partners

- **State Health Society Bihar**: All the Doctors and supporting staff in government pay rolls, working at the District Hospital and Primary Health Centres
- **Rajendra Memorial Research Institute of Medical Sciences** Patna, as one the site and support in training
- **Médecins Sans Frontières-Spain,** implementing partner in Vaishali district
- **Drugs for Neglected Diseases initiative** as facilitating the pilot by training, monitoring and management
- The project was fully supported by the **ICMR, NVBDCP** and **DCGI**

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Objectives

- Determine **effectiveness (including 12 month outcome) and safety profile of 3 new treatment regimens under real field conditions**
- Provide **evidence based recommendations** for policy makers

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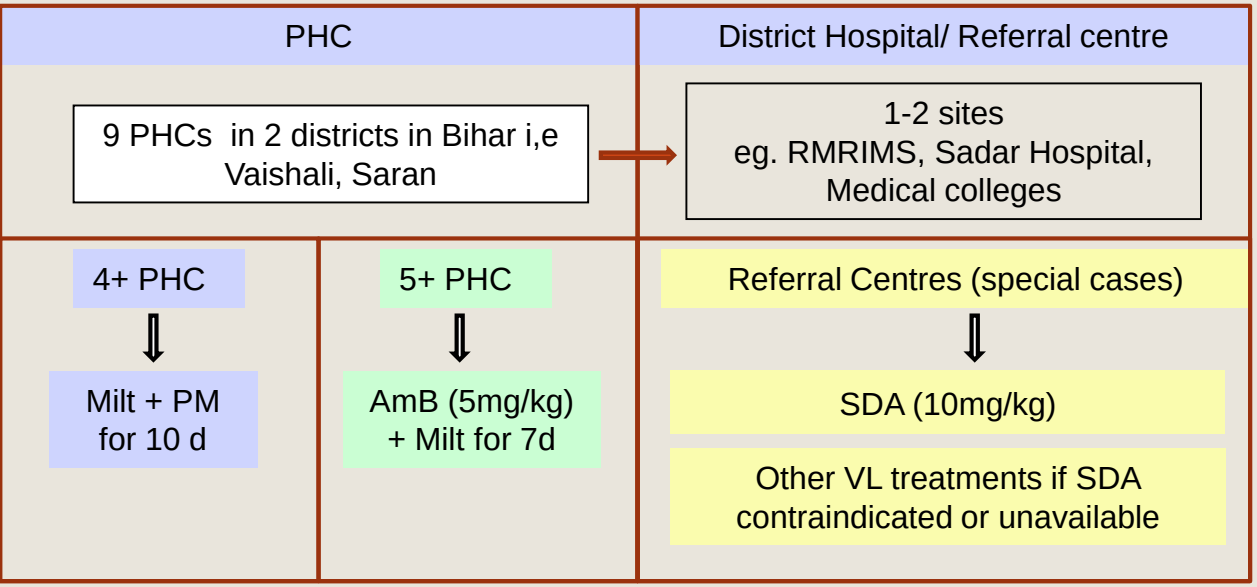
Pilot Implementation Study - India

Open label, prospective, non randomised, non comparative, multicentre study in public hea

Regimens: Single
10mg/kg
Milt (2.5mg/Kg/d) +
AmB (5mg/kg SD)

- Treatment by Government doctors/staff except Hajipur
- Training: GCP + KA case management
- Upgradation of health centers e.g lab, ILR, drugs, diagnostic kits
- IEC team: training of ASHA

PROJECT DESIGN



Ethical clearance: RMRIEC, MSF-ERB, LSHTM

Assessment at 6 mnth and 12 mnth

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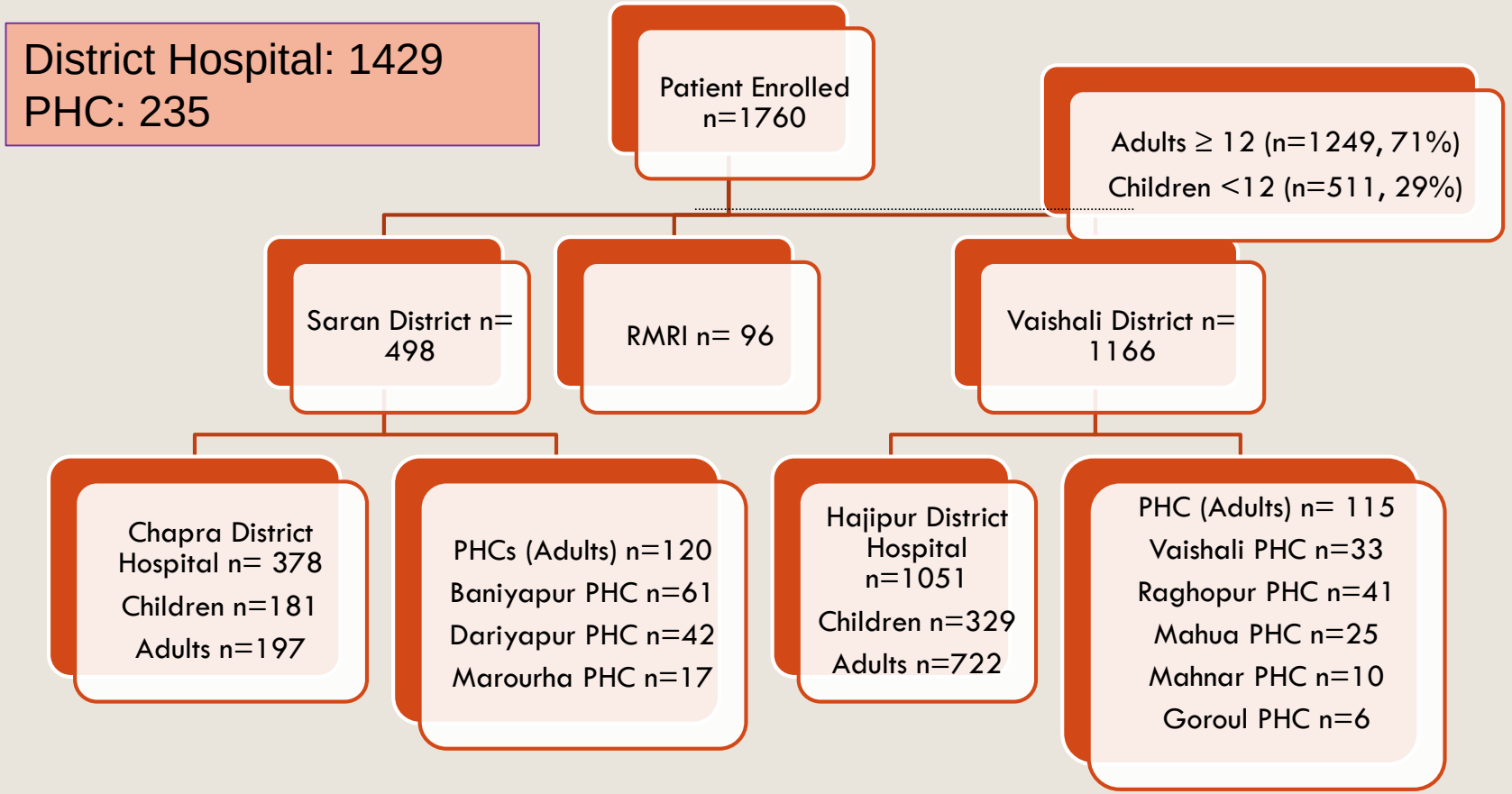
Enrolment (n=1760) Aug 2012-Oct 2014



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Characteristics Children < 12 years(1)

	SD AmB N=260	AmB + MF N=72	MF + PM N=179
	Number (%)	Number (%)	Number (%)
Sex			
Female	121 (46.5%)	32 (44.4%)	76 (42.5%)
Male	139 (53.5%)	40 (55.6%)	103 (57.5%)
Duration of illness			
≤8 weeks	225 (86.5 %)	66 (91.7%)	134 (74.9)
>8 weeks	35 (13.5%)	06 (8.23)	45 (25.1%)
Hemoglobin, g/dL			
<6	**39 (15.0 %)**	06 (8.3 %)	04 (2.2 %)
6–8	114 (43.8 %)	23 (31.9 %)	42 (23.5 %)
>8	107 (41.2%)	43 (59.7 %)	133 (74.3 %)
normal range 12 -14	01	02	01
Serum Creatinine <1 mg/dl is normal range			
<1	258 (99.2 %)	72 (100%)	178 (99.4 %)
≥1-≤2	02 (0.8%)	0	01 (0.6 %)
>2	**04 (1.7 %)**	0	0

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Characteristics Children < 12 years (2)

	SD AmB N=260	AmB + MF N=72	MF + PM N=179
	Number (%)	Number (%)	Number (%)
SGPT (ALT) <48 U/L normal , >48 elevated level			
<48	198 (76.2 %)	45 (62.5 %)	131 (73.2%)
>48-200	58 (22.3 %)	21 (29.2%)	44 (24.6%)
>200	04 (1.5%)	6 (8.3 %)	04 (1.5%)
SGOT (AST) <46 U/L normal , >46 elevated level			
<46	100 (38.5 %)	24 (33.3 %)	71 (39.7 %)
> 46-200	136 (52.3 %)	37 (51.4 %)	93 (52.0%)
>200	24 (9.2 %)	11 (15.3 %)	15 (8.4 %)
Nutritional status			
Normal	246(94.6%)	70(97.2%)	161(89.9%)
Moderate acute malnutrition	13(5%)	1(1.4%)	11(6.1%)
Severe acute malnutrition	1(0.4%)	1(1.4%)	**7(3.9%)**

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Characteristics Adults > 12 years (1)

	SD AmB n=631	AmB + MF n=285	MF + PM n=333
	Number (%)	Number (%)	Number (%)
Sex			
Female	259 (37.5%)	79 (27.7%)	125 (37.5%)
Male	372 (59.0%)	206 (72.3%)	208 (62.5%)
Duration of illness			
≤8 weeks	471 (74.6%)	221 (77.5%)	270 (81.1%)
>8 weeks	160 (25.4%)	64 (22.5%)	63 (18.9%)
Hemoglobin, g/dL : normal range 12 -14			
<6	**48 (7.6%)**	13 (4.6%)	10 (3.0%)
6–8	191 (30.3%)	71 (24.9%)	72 (21.6%)
>8	392 (62.1%)	201 (70.5 %)	251 (75.4 %)
normal range 12 -14	37 (5.9)	28 (9.8)	31 (9.3)
Serum Creatinine	<1 mg/dl is normal range		
<1	499 (79.1 %)	227 (79.6 %)	250 (75.1%)
≥1-≤2	98 (19.1 %)	56 (19.6%)	82 (24.6%)
>2	**1 (0.3%)**	**02 (0.7%)**	**01 (0.3%)**

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Characteristics Adults > 12 years (2)

	SD AmB n=631	AmB + MF n=285	MF + PM n=333
	Number (%)	Number (%)	Number (%)
SGPT (ALT) <48 normal , >48 elevated level			
<48	405 (64.2 %)	162 (56.8%)	214(64.3 %)
>48-200	199 (31.5%)	112 (39.3 %)	112 (33.6 %)
>200	27 (4.3 %)	11 (3.9 %)	07 (2.1%)
SGOT (AST) <46normal , >46 elevated level			
<46	217 (34.4 %)	92 (32.3 %)	168 (50.5 %)
> 46-200	348 (55.2%)	161 (56.5%)	147 (44.1%)
>200	66 (10.5%)	32 (11.2%)	18 (5.4 %)
Nutritional status			
Normal	537(85.1%)	265(93%)	274(82.3%)
Moderate acute malnutrition	78(12.4%)	18(6.3%)	44(13.2%)
Severe acute malnutrition	16(2.5%)	2(0.7%)	15 (4.5%)

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Results – Initial Outcome (n = 1760)

	SD AmB	AmB+MF	MF + PM
Number of patients started on treatment (n=1760)	891	357	512
Initial cure at day 10 (%) (95% CI)	884 (99.2%) (95%CI-98.6-99.8)	354 (99.2%) (CI-98.3 – 100.0)	508 (99.2 %) (CI-98.4- 99.9)

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Results- Final Outcome (Worst Case Analysis)

	SD AmB	AmB+MF	MF + PM
Number of patients followed up at 6 mnth(n=1760)	891	357	512
Cure at 6 month	810 (90.9%) (95%CI-89.0-92.8)	317 (88.8%) (95%CI-85.5-92.1)	497 (97.0%) (95%CI-95.6-98.5)
Relapse rate (n=64)	43 (4.8%)	19 (5.3%)	2 (0.4%)
Defaulter	0	1	4
Lost to Follow Up (n=61)	34	18	9
Treatment stopped by doctor for side effects	4	2	0
Number of patients followed up at 12 months (n=1343) (Interim Data)	695	290	358
Relapse Rate (n =11)	2 (0.3%)	6 (2%)	3 (0.8%)
Lost To Follow Up (n= 92)	50	16	26

Adverse Events

	SD AmB N=891	LAmB + MF N=357	MF + PM N=512
Total Adverse Events Reported	174 (19.5%)	137 (38.4%)	123 (24%)
No. of subjects with at least one AE n(%)	133 (14.9%)	90 (25.2%)	92 (18%)
Drug Related Serious Adverse Events n(%)	2* (0.5)	0 (0)	0 (0)
Non-Drug Related Serious Adverse Events n(%)	3** (0.7)	0 (0)	0 (0)

AE captured during start of treatment to EOT
* Allergic reaction + Atrial ectopic. Both resolved
** Pneumonia, Empyema, Urinary Tract Infection. All resolved

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Limitations of Study

- Children **not** treated at Primary Health Centre level and treated at District Hospital only as per regulatory recommendation
- Patients admitted and provided treatment at Saran District Hospital for MF/PM
- Patients referred from PHC/Saran District Hospital to higher centre for parasitology
- Biochemistry tests done only at District Hospital

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Conclusion and Recommendations

- Combination regimens and SDA are safe and effective treatment in public health sector at field level and feasible to implement at large scale to facilitate VL elimination

- Indian National program revised policy in Sep 2014
  - Single Dose Ambisome as first option
  - MF/PM Combination as second option

- Combination regimen to be choice of treatment at sites where cold chain cannot be deployed

- Relapses continue to occur after 6 month post treatment, need to Follow up patients for 12 month within national program in region to generate further evidence on relapse

- Cohort Event Monitoring should be strengthened at all sites in India to document long term outcome data and adverse event to identify relapse, PKDL, treatment failure, AEs

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Acknowledgement

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- All Government Doctors, staff involved in study

State Health Society Bihar

RMRIMS - Patna

NVBDCP

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THANK YOU

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