Diversity of kala-azar treatment in different regions and disease niches

Dr Suman Rijal, MBBS, MRCP (UK), FRCP, PhD
Director,
Drug for Neglected Diseases India

Pune
1-3 Sept. 2017
Visceral Leishmaniasis

- **Life-threatening** protozoan parasitic disease transmitted by the phlebotomus sandfly

- **Incidence Estimates**- An estimated 50,000 to 90,000 new cases of VL occur each year (http://www.who.int/)

- In 2015, more than **90% cases reported from seven countries**: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan.

- **Population at risk**: 616 million population in endemic areas.

- **Etiology**:
  - *L. donovani*: Indian subcontinent and East Africa
  - *L. infantum*: Mediterranean basin, Central and South America

- **Key strategies for control in South Asia**:
  - Early diagnosis and appropriate treatment
  - Integrated Vector Control
Visceral Leishmaniasis Global Situation

Status of endemicity of visceral leishmaniasis, worldwide, 2013

Number of new VL cases reported, 2013

- >1,000
- 500–999
- 100–499
- <100
- 0
- No autochthonous cases reported
- No data
- Not applicable

Countries reported imported VL cases
- Saudi Arabia: 8
- Russian Federation: 2
- Belgium: 1
- Finland: 1
- Republic of Moldova: 1

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2015. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

http://gamapserver.who.int/mapLibrary/Files/Maps/Leishmaniasis_2013_VL.png
New treatments: last 15 years.

1922
Penta-valent Antimonials

Since 1980’s
Amphotericin B

2002
miltefosine

2006
Paromomycin

- 1996 Registered at FDA 1996
- 2010  SDA Recommended by WHO
- 2011  Donation by Gilead
- 2014  Recommended in National prog.
SSG failure rates in India: 1980 to 1997

- Emergence of antimony-resistant *L. donovani* strains in India. *Lira et al, 1999*
- Antimony resistant strains of *L. donovani* were wide spread over different geographical areas in Bihar. *Thakur et al, 2004*
- Associated with severe toxicity and high death rates: No longer recommended in South Asia

**East Africa: Pentavalent antimonials**- More than 90% efficacy. *Musa et al 2012*
- SSG and PM (17-day regimen) - Mainstay of therapy for immunocompetent

**Brazil** (Romero et al 2017)
- meglumine antimoniate (20 mg/kg for 20 days): 77.5% cure at 6 months
- MA + LAMB: 84% cure at 6 months
# Efficacy of miltefosine monotherapy in South Asia

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Country</th>
<th>No.</th>
<th>Final cure (95% CI)</th>
<th>Relapse rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jha 1999</td>
<td>India</td>
<td>30*</td>
<td>96.7 [90.2, 103.1]</td>
<td>3.3 [-3.1, 9.8]</td>
</tr>
<tr>
<td>Sundar 2005</td>
<td>India</td>
<td>299</td>
<td>94.3 [91.7, 96.9]</td>
<td>3.0 [1.1, 4.9]</td>
</tr>
<tr>
<td>Bhattacharya 2007</td>
<td>India</td>
<td>1132</td>
<td>81.9 [79.6, 84.1]</td>
<td>3.9 [2.8, 5.0]</td>
</tr>
<tr>
<td>Rahman et al 2011</td>
<td>Bangladesh</td>
<td>977</td>
<td>85 (per protocol)</td>
<td></td>
</tr>
<tr>
<td>Sundar 2012</td>
<td>India</td>
<td>567</td>
<td>90.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Rijal 2013</td>
<td>Nepal</td>
<td>120</td>
<td>82.5 (6 mt)</td>
<td>10.8 (5.2, 16.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73.3 (12 mt)</td>
<td>20.0% (12.8, 27.2)</td>
</tr>
</tbody>
</table>
Treatment failure with miltefosine

- Relapse in up to one-fifth of the MIL-treated patients observed.  
  Sunnar, 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
Miltefosine use outside South Asia

- Sudan & Kenya: Phase II study. (Wasunna 2016)

<table>
<thead>
<tr>
<th>Country</th>
<th>AmBisome + SSG</th>
<th>AmBisome + Miltefosine</th>
<th>Miltefosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan</td>
<td>21/24 (88%)</td>
<td>17/24 (71%)</td>
<td>18/27 (67%)</td>
</tr>
<tr>
<td>Kenya</td>
<td>26/27 (96%)</td>
<td>23/25 (92%)</td>
<td>20/24 (83%)</td>
</tr>
</tbody>
</table>

- Ethiopia: Immunocompetent VL: 75.6% cure rate
- Miltefosine safer but less effective than SSG in a population with a high prevalence of HIV. Ritmeijer et al 2006
- Mediterranean region and Latin America: reliable data on the efficacy of miltefosine have not been published.
Recommended regimes of LAMB: variation with endemic areas (WHO Technical Report Series 949 (2010))

<table>
<thead>
<tr>
<th>Region</th>
<th>Etiology</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean Basin, Middle East, Central Asia, South America</td>
<td><em>L. infantum</em></td>
<td>3–5 mg/kg per day in 3–6 infusions, up to a total dose of <strong>18–21 mg/kg</strong></td>
</tr>
<tr>
<td>East Africa (Ethiopia, Eritrea, Kenya, Somalia, Sudan and Uganda) and Yemen</td>
<td><em>L. donovani</em></td>
<td>3–5 mg/kg per day by infusion over 6–10 days up to a total dose of <strong>30 mg/kg</strong></td>
</tr>
<tr>
<td>Bangladesh, Bhutan, India and Nepal</td>
<td><em>L. donovani</em></td>
<td>3–5 mg/kg over 3–5 days up to a total dose of <strong>15 mg/kg</strong> by infusion (A) or <strong>10 mg/kg</strong> as a single dose by infusion</td>
</tr>
</tbody>
</table>
### Single Dose LAMB (AmBisome®) in Indian Kala-azar

<table>
<thead>
<tr>
<th>Total Dose mg/kg</th>
<th>No. of Patients*</th>
<th>Treat. Dur.</th>
<th>Cure Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>17</td>
<td>1</td>
<td>100 (Thakur 2001)</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>1</td>
<td>91 (Sundar, BMJ 2002)</td>
</tr>
<tr>
<td>7.5</td>
<td>203</td>
<td>1</td>
<td>90 (Sundar 2003)*</td>
</tr>
<tr>
<td>10</td>
<td>304</td>
<td>1</td>
<td><strong>96 (Sundar 2010)</strong></td>
</tr>
<tr>
<td>10</td>
<td>300</td>
<td>1</td>
<td>97 (Mondal 2014)</td>
</tr>
<tr>
<td>10</td>
<td>158</td>
<td>1</td>
<td>98 (Rahman 2017)</td>
</tr>
<tr>
<td>10</td>
<td>891</td>
<td>1</td>
<td>94.6 (unpublished)* +</td>
</tr>
</tbody>
</table>

- Multicenter
- Relapse 6.4%
LAMB in East Africa

- Study terminated after interim analysis due to low efficacy. *Khalil et al 2014*
  - SD 7.5 mg/kg: 40%
  - SD 10 mg/kg: 58%
  - 3 mg/Kg for 7 days: 85%

- AmBisome recommended for complicated primary VL cases, patients with VL relapse and patients with contraindications to antimonials or PM

LAMB in Brazil:

Multicentre randomized (Romero et al 2017)

- LAMB (3 mg/kg/day for 7 days). 109 pt: **87.2%**
- LAMB (10 mg/kg SD) plus MA (20 mg/kg for 10 d) 112 pt: **83.9%**
Combination treatments

• Combination treatments: Sb$^+$ + Paro. established in Africa and India (Chunge et al 1990, Thakur et al 1995, 2000, Seaman et al 1993)

• **Phase III RCT:** Combination with SD LAMB, mil or paro
  - **India** (Sundar 2011): over 97% cure rates
  - **Bangladesh** (Rahman 2017): None of the combinations were inferior to LAMB

• Pilot implementation study in India: SDA, A+M and M+P.
  - 1761 patients treated at DH and PHC
  - around 95% or more cure rates in all 3 regimens.

• **Phase II Randomized Trial in Sudan and Kenya:** All less than 90%.
  - LAMB + SSG: 87%
  - LAMB + Miltefosine: 77%
  - Miltefosine Monotherapy: 72%
Treatment: HIV-VL coinfection

- **WHO recommendation**: 40mg/kg AmBisome for co-infection: based on case series from Europe with *L. infantum*
- Study from Ethiopia 30 mg /kg:
  - 32% of patients had parasites seen on Test of Cure despite initial clinical improvement
  - After relapse, the efficacy of repeated treatment reduced
- RCT ongoing in India combination of AmBisome® total dose 30mg/kg plus miltefosine 100mg for 14 days, and AmBisome® total dose 40mg/kg alone.
Sustenance of elimination and zero transmission

Reservoirs for Leishmania transmission in South Asia

- Visceral leishmaniasis
- Post kala-azar dermal leishmaniasis
- HIV-VL co-infection
- Asympto. Leishmania infection

- Need for understanding the role in Leishmania transmission
- Need for better tools: diagnostics, drugs and ? vaccines
Summary

• Efficacy of different drugs vary in the different regions and age groups

• Treatment with LAMB and combination regimens have shown excellent cure rates and safety in South Asia

• East Africa: SSG monotherapy or plus PM currently recommended regimens

• Further evidence is needed to be generated e.g. define the optimal dose of LAMB in EA; regimens for HIV-VL coinfection in Asia

• Better tools would possibly needed if we want to go for zero transmission.
Acknowledge all our partners