Visceral Leishmaniasis treatment access: The reality on the ground

Margriet den Boer
KalaCORE Regional Coordinator, East Africa

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SSG+PM introduction in Africa: history

- **1992-1994:** First clinical studies conducted by MSF in South Sudan investigating the effectiveness of a new combination treatment under field conditions (SSG+PM).
- **2007:** Publication of retrospective analysis of the use of SSG+PM vs SSG alone in South Sudan, concluding that SSG+PM is both safer and more effective in remote field settings.
- **2012:** Publication of a DNDi multi-centre trial of the efficacy of SSG+PM combination therapy. SSG+PM and SSG alone were shown to have a similar efficacy and safety.
- **From 2012 on:** acceptance of SSG+PM in national policies
- **2014:** DNDi SSG+PM multi-country pharmacovigilance studies demonstrated excellent safety.
Taking stock

Years after introducing SSG+PM in national protocols and guidelines in East Africa and roll out, did we achieve:

- Country-wide uptake
- Continuous availability of drugs and diagnostics
- Safe use of drugs: precautions and monitoring
- Trained human resources
- Hospital readiness
- Access to treatment for all patients
- All conditions for patients met (shelter, food, RUTF)
- Tackling HIV/VL
Most important access barriers East Africa

• Extremely remote and/or insecure areas
• Dependency on NGO’s/WHO for drug supply
• Patients first seek care from traditional healers and present in very late stage of disease
• Low awareness among health workers
• Staying away from home/work causes great losses
ACCESS TO TREATMENT FOR LEISHMANIASIS as judged by countries

- Insufficient access
- Good access
Conditions for implementation

• Getting the basic epidemiology straight

<table>
<thead>
<tr>
<th></th>
<th>Reported</th>
<th>Estimated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan</td>
<td>3742</td>
<td>15,700-30,300</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1860</td>
<td>3,700-7,400</td>
</tr>
</tbody>
</table>

• Purchase not just the drugs but the whole delivery system
• Involve, educate and motivate health workers and all other stakeholders on the ground
• Focus on sustainable structures and financing for all aspects of implementation
• Continued operational research to fill gaps: mapping, access, innovative control approaches
KalaCORE

• UK commitment to NTD’s; DFID bid for “Tackling VL in South Asia and East Africa” Project - £ 27.3 million for 5 years (until April 2019) Target countries:
  • South Asia: India, Bangladesh, Nepal
  • East Africa: Sudan, South Sudan, Ethiopia

KALACORE Consortium for Control and Elimination of Visceral Leishmaniasis in South Asia and East Africa (2014-18)
KalaCORE plans

- Supply of drug and diagnostics and supporting their immediate road transport
- Central drug buffer stocks in case of outbreaks
- Human resources gap: sustainable university-based training programs and clinical mentoring
- VL-focused health facility checks and subsequent upgrade
- Advocacy for food aid
- Operational research on vector control and access
- Analysis of disease data at hospital level including retrospective review
Standardized VL treatment facility checks

Assessments together with MoH; standards defined by WHO

Findings:
• Recent stock gaps of VL drugs and diagnostics in >50% of facilities;
• Wide-spread protocol non-adherence;
• Incomplete reporting;
• Shortage or absence of staff trained in VL;
• Laboratory not equipped for VL testing;
• Patients wards not meeting basic standards;
<table>
<thead>
<tr>
<th>Compound</th>
<th>Commercial name and manufacturer</th>
<th>Price information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal amphotericin B (L-Amb)</td>
<td><em>AmBisome®, Gilead, US</em></td>
<td>DONATION or WHO negotiated price: 18 USD/50 mg vial</td>
</tr>
<tr>
<td>Miltefosine (MF)</td>
<td><em>Impavido®, Paladin, Canada</em></td>
<td>WHO negotiated price (status?)</td>
</tr>
<tr>
<td></td>
<td><em>Single-source</em></td>
<td>For adults: 45.28 - 54.92 Euro for 56 (50mg) capsules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For children: 34.36 - 39.3 Euro for 56 (10mg) capsules</td>
</tr>
<tr>
<td>Paromomycin (PM)</td>
<td><em>Paromomycin, Gland Pharma, India</em></td>
<td>App. price 15 USD per adult course of 21 days</td>
</tr>
<tr>
<td>WHO approved generic sodium stibogluconate (SSG)</td>
<td><em>SSG, Albert David, India</em></td>
<td>5.65 Euro/30 ml vial 100 mg/ml</td>
</tr>
<tr>
<td>Meglumine antimoniate (MA)</td>
<td><em>Glucantime®, Sanofi</em></td>
<td>WHO negotiated price 1.2 USD/5 ml vial 85 mg/ml</td>
</tr>
</tbody>
</table>
Creating conditions for **drug access**: Risk management

- **Sustainability is key:**
  - Country registrations
  - Continued production/multiple producers
  - Stable pricing
  - Assured quality

- None of which are completely in place today
- Efforts by stakeholders have been scattered and partially effective
- Extremely high dependency on single source AmBisome, paromomycin
Paromomycin (PM)

- Originally marketed in the 1960’s as IV antibiotic
- Further developed for VL by WHO and BMGF Foundation (iOWH) and registered in India in 2006
- Clinical multicentre study and PV by DNDi and registration facilitated by DNDi
- Produced by Gland Pharma in India. **Quality problems leading to supply gaps** have occurred in the past
- Price is low but **long term sustainability is a concern**
- No forecasting mechanism and no buffer stocks except those held by MSF and DNDi – **lead times can be very long**
- **Ownership dossier** is unclear and no agreements are in place
Miltefosine (MF)

- Originally developed for breast cancer and developed with public funds through WHO/TDR for VL
- Reduced place in therapy (WHO expert Committee 2010) – current consumption foreseen to remain low. **No binding agreements on price and sustainability of production**: dependency on goodwill Paladin despite existing MoU with WHO.
- WHO negotiated price for large quantities – **no agreement on preferential price for small orders**. Currently >250 USD per single Tx for non profit sector and >2000 USD for private market.
- No forecasting mechanism and very small buffer stock held by Paladin – **lead times can be long (3-6 months)**
# Drug registrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Asia (India, B’desh)</th>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBisome (Gilead Sc. India)</td>
<td>Registered in India and Bangladesh</td>
<td>Not registered in Sudan, Ethiopia, Kenya, Uganda</td>
</tr>
<tr>
<td>Generic SSG (Albert David, India)</td>
<td>n.a.</td>
<td>Registered in Sudan, Uganda. Not registered in Ethiopia, registration expired in Kenya</td>
</tr>
<tr>
<td>Paromomycin (Gland Pharma, India)</td>
<td>Registered in India Not registered in Bangladesh</td>
<td>Registered in Uganda, Kenya. Not registered in Sudan and Ethiopia; both in process *</td>
</tr>
<tr>
<td>Miltefosine (Paladin, Canada)</td>
<td>Registered in India, Bangladesh</td>
<td>Not registered in Sudan, Ethiopia, Kenya, Uganda</td>
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</table>

* With DNDi facilitation
Way forward: drug access strategy

• Agreements with manufacturers are key; these are not in place
  – AmBisome donation must be sustained
  – Creating goodwill to sustain production: providing pooled demand forecasts, supporting registrations, support in achieving WHO GMP standards
  – Better coordination and division of roles among stakeholders
    • Governments endemic countries: forecasting, drug financing
    • DNDi: supporting drug licensing and registration
    • MSF: advocacy/exposure
    • WHO: GMP inspections, legal agreements on maintaining production and low prices, central buffer stocks
With thanks to:

KalaCORE

DNDi AFRICA
Drugs for Neglected Diseases initiative

Many thanks to DNDi for my travel grant