Translating treatment options to control programs

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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 per region

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
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)
Example: 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 training programs and clinical mentoring
• VL-focused health facility checklist and subsequent upgrade
• Advocacy for food aid
• Operational research on vector control and access
• Analysis of disease data at hospital level including retrospective review
<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>AmBisome®, Gilead, US</td>
<td>DONATION or WHO negotiated price: 18 USD/50 mg vial</td>
</tr>
<tr>
<td></td>
<td>Single-source</td>
<td></td>
</tr>
<tr>
<td>Miltefosine (MF)</td>
<td>Impavido®, Paladin, Canada</td>
<td>WHO negotiated price (status?)</td>
</tr>
<tr>
<td></td>
<td>Single-source</td>
<td>For adults: 45.28 - 54.92 Euro for 56 (50mg) capsules</td>
</tr>
<tr>
<td></td>
<td>Price status uncertain</td>
<td>For children: 34.36 - 39.3 Euro for 56 (10mg) capsules</td>
</tr>
<tr>
<td>Paromomycin (PM)</td>
<td>Paromomycin, Gland Pharma, India</td>
<td>App. price 15 USD per adult course of 21 days</td>
</tr>
<tr>
<td></td>
<td>Single-source</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Price status uncertain</td>
<td>Ownership dossier?</td>
</tr>
<tr>
<td>WHO approved generic sodium stibogluconate (SSG)</td>
<td>SSG, Albert David, India</td>
<td>5,65 Euro/30 ml vial 100 mg/ml</td>
</tr>
<tr>
<td></td>
<td>Single-source</td>
<td></td>
</tr>
<tr>
<td>Meglumine antimoniate (MA)</td>
<td>Glucantime®, Sanofi</td>
<td>WHO negotiated price</td>
</tr>
<tr>
<td></td>
<td>Single-source</td>
<td>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 and 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 and long term sustainability is a concern
- No forecasting mechanism and no buffer stocks except those held by MSF and DNDi – lead times are very long
- Ownership dossier is unclear and no agreements 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
- 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 (Ethiopia, Sudan)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AmBisome</strong></td>
<td>Registered in India and Bangladesh</td>
<td>Not registered in Sudan and Ethiopia</td>
</tr>
<tr>
<td>(Gilead Sc. India)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generic SSG</strong></td>
<td>n.a.</td>
<td>Registered in Sudan</td>
</tr>
<tr>
<td>(Albert David, India)</td>
<td></td>
<td>Not registered in Ethiopia</td>
</tr>
<tr>
<td><strong>Paromomycin</strong></td>
<td>Registered in India</td>
<td>Not registered in Sudan and Ethiopia</td>
</tr>
<tr>
<td>(Gland Pharma, India)</td>
<td></td>
<td>both in process *</td>
</tr>
<tr>
<td><strong>Miltetofosine</strong></td>
<td>Registered in India, Bangladesh</td>
<td>Not registered in Sudan and Ethiopia</td>
</tr>
<tr>
<td>(Paladin, Canada)</td>
<td></td>
<td>no progress</td>
</tr>
</tbody>
</table>

* With DNDi facilitation
Way forward: drug access strategy

- Agreements with manufacturers are key
  - 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— who is doing what? Eg:
    - DNDi: supporting drug licensing and registration
    - MSF: advocacy/exposure
    - WHO: GMP inspections, legal agreements on maintaining production
- Define and assure own responsibilities of countries are met after NGO program hand-over
- ?
With thanks to:

DNDi
KalaCORE
MSF

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