ACCESS TO QUALITY-ASSURED MEDICINE FOR NEGLECTED TROPICAL DISEASES:

A case study of miltefosine for leishmaniasis

Temmy Sunyoto, MD MPH
Neglected Tropical Diseases

- WHO: a diverse group of communicable diseases that prevail in tropical and subtropical conditions
- = diseases of poverty

- Repackaging of global health

+ Mycetoma, chromoblastomycosis and other deep mycoses
+ Snakebite envenoming
+ Scabies and other ectoparasites
Fatal imbalance in R&D

756 products developed
(excluding vaccines & biologicals) (2000-2011)*

- Neglected tropical diseases (NTDs)
- Others (Central nervous system, cardiovascular, etc.)


Leishmaniasis

- A parasitic Neglected Tropical Disease
- Caused by >20 Leishmania parasite
- Transmitted by Phlebotomine sandflies
- Anthroponootic or zoonotic
- Clinical spectrum: CL, MCL, VL or Kala azar – fatal without treatment
Global burden of VL 2015

Countries reporting imported VL cases:
- Ethiopia - 73
- Nepal - 15
- France - 10
- Greece - 6
- Yemen - 5
- Argentina - 3
- Georgia - 3
- Iraq - 3
- Morocco - 2
- Israel - 1
- Jordan - 1
- Russian Federation - 1
- Saudi Arabia - 1
- Thailand - 1

Map of the world showing the distribution of visceral leishmaniasis cases with percentages indicating the proportion of new cases reported in different regions.
Control (and elimination) of VL

- Control options for VL:
  - Early diagnosis and treatment
  - Vector control
  - Control of animal reservoir
  - Environmental measures
  - (Vaccination)

- 2005 MoU: Bangladesh, India & Nepal elimination by 2015
- 2014 MoU: Bangladesh, Bhutan, India, Nepal, Thailand & SEAR elimination by 2017

<table>
<thead>
<tr>
<th>Drug</th>
<th>Commercial names and manufacturer</th>
<th>Unit</th>
<th>Price information</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium stibogluconate</td>
<td>Pentostam®: GSK, Generic: Albert David</td>
<td>30 ml vial of 100 mg/ml</td>
<td>$6.45</td>
<td>Injectable, high toxicity, resistance</td>
</tr>
<tr>
<td>Meglumine antimoniate</td>
<td>Glucantime®, Aventis</td>
<td>5 ml vial of 81 mg/ml</td>
<td>WHO-negotiated price: $1.2</td>
<td>As above</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>Various</td>
<td>50 mg vial</td>
<td>Variable ~$ 7.5 per 50-mg vial</td>
<td>Injectable, high toxicity</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>AmBisome®: Gilead</td>
<td>50 mg vial</td>
<td>Access price $18</td>
<td>Low toxicity, requires cold chain - stable up to 25°C</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>Impavido®: Knights Therapeutics</td>
<td>50 mg and 10 mg tablet-pack of 56</td>
<td>€100-140</td>
<td>Adverse effect, teratogenicity</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Generic: Gland Pharma</td>
<td>2 ml vial of 375 mg/ml</td>
<td>€1.3</td>
<td>Injectable, side effects</td>
</tr>
</tbody>
</table>
A PPP success story

• Miltefosine (Impavido®)
• Originally developed as anti-cancer agent
• 1987: discovery in vitro anti-leishmanial activity
• Excellent oral bioavailability in mouse models
• Candidate compound for human VL
• 1995: Public Private Partnership: WHO/TDR - Asta Medica – Indian researchers
**Drug discovery and development**

**Milestones**

- **1980**: MLF discovered to have anti-leishmanial activity *in vitro* and *in vivo*
- **1990**: Pre-clinical development by academia in Germany and UK
- **2002**: March 2002: MLF registered as the first oral drug for VL in India

**Ownership**

- **ASTA MEDICA**
- **Æterna Zentaris**

**Transaction**

- **1998-2002**: MoU between WHO/TDR-AstaMEDICA India to develop MLF for VL
- **2002**: March 2002: MLF registered as the first oral drug for VL in India
- **2011**: MLF included in the WHO EML
- **2013**: November: Endo acquired Paladin Labs for US$ 1.6 billion
- **2016**: 2016 licensed for US market

**Drug R&D phase**

- **1990**: MoU between WHO/TDR-AstaMEDICA India to develop MLF for VL
- **2002**: March 2002: MLF registered as the first oral drug for VL in India
Access issue #1: Cost

- Public health needs: cost should not exceed US$50-60/treatment
- Miltefosine first became available in private market in India for US$150-200/tx
- Long negotiation over public price – known as WHO-negotiated price
- **BUT:** minimum order quantity was imposed (75,000 caps and later 200,000 caps or equal to 3500 treatment courses)
- Price keeps increasing
**Access issue #1: Cost**

<table>
<thead>
<tr>
<th>Price policy</th>
<th>Price per full course</th>
<th>Period covered</th>
<th>Remark</th>
</tr>
</thead>
</table>
| Preferential price for public or non-profit sector in developing countries | €45.3-54.9 (US$54-64)
€80-110 (US$94-130) | 2002 – 2008 | Price varied based on quantity purchased; minimum order quantity/MOQ was imposed |
|                                                        | €100-140 (US$117-164) | 2016 onwards | No MOQ, but price still varied based on quantity                       |
| Market price EU                                       | €3000-12000            | 2012          | Direct order to the producer/distributor                               |

*One full adult course of miltefosine monotherapy uses one pack containing 56 caps. The recommended dose is 2.5 mg/kg daily for 28 days (roughly 50 mg capsule bid for adults weighing >25 kg).*

\(^a\) This is the original price aimed for in the agreement between WHO and AstaMedica (1995) and published officially in the latest WHO Control of Leishmaniasis guidelines (2010)

\(^b\) Price quoted by Knight Therapeutics for purchase by non-profit organizations Médecins Sans Frontières (MSF)

\(^c\) For 28 caps, see https://www.drugs.com/price-guide/impavido
Access issue #2: Availability

- Difficulties to obtain preferential price impacts availability in endemic countries
- Minimum order quantity led to oversupply and wastage
- Long production lead-time at the manufacturer
- Insecure supply – frequent stock-outs
- Bureaucratic tender mechanisms for public procurement
- Access difficulties in each region (Asia, Africa, Europe, North America, Latin America)
- Compassionate use or donation exist, yet little known
MLF was discovered to have anti-leishmanial activity in vitro and in vivo.

1980: MLF – discovered to have anti-leishmanial activity under preclinical development by academia in Germany and UK.

1990: MoU between WHO/TDR-AstaMEDICA India to develop MLF for VL.


2002: MLF registered as the first oral drug for VL in India. March 2002:

2004: MLF was granted orphan drug designation by the US FDA.

2006: Ph IV trial (India) and MLF monotherapy as 1st line for VL in Indian sub-continent for Elimination Programme.

2008: March 2008: Zentaris sole MLF rights to Paladin for US$ 8.5 million.

2008: Endo acquired Paladin Labs for US$ 1.6 billion.

2011: March 2011: MLF included in the WHO EML.

2014: February 14: Registration of MLF by US FDA and PRV granted.

2016: Knight retained Impavido® from Paladin.

Zentaris AG and Aeterna Zentaris

Knight

Endo

February 2014. Knight retained Impavido® from Paladin.

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Access issue #3: Quality

- Often forgotten
- Procurement and accessibility issues led Bangladeshi program to opt for locally sourced and less expensive product
- Cluster of VL deaths followed
- On investigation, it was counterfeit, without active ingredients

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**Drug discovery and development**

**Post – registration / Post marketing approval**
A US law created in 2007 as incentive for R&D for NTD and rare pediatric diseases

- Some loopholes:
  - Drugs that have been used outside the US for some time
  - Recipient may have no role in R&D
  - No guarantee for better access

### Table. Awarded Priority Review Vouchers, September 2008 to August 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Sponsor</th>
<th>Disease</th>
<th>Sold</th>
<th>Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neglected tropical diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemether-lumefantrine</td>
<td>2009</td>
<td>Novartis</td>
<td>Malaria</td>
<td>No; used internally</td>
<td>Canakunimab for gouty arthritis in 2011</td>
</tr>
<tr>
<td><strong>Bedaquiline</strong></td>
<td>2012</td>
<td>Johnson &amp; Johnson</td>
<td>Multidrug-resistant Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miltefosine</td>
<td>2014</td>
<td>Knight Therapeutics</td>
<td>Leishmaniasis</td>
<td>$125 million to Gilead Sciences, 2014</td>
<td></td>
</tr>
<tr>
<td><strong>Rare pediatric diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholic acid</td>
<td>2015</td>
<td>Asklepion®</td>
<td>Bile acid synthesis disorders involving single-enzyme defects and peroxisomal disorders</td>
<td>$245 million to Sanofi, 2015</td>
<td></td>
</tr>
<tr>
<td>Dinutuximab</td>
<td>2015</td>
<td>United Therapeutics</td>
<td>High-risk neuroblastoma</td>
<td>$350 million to Abbvie, 2015</td>
<td></td>
</tr>
</tbody>
</table>

Lessons learned

- Miltefosine is a **major therapeutic advance** for leish - will remain valuable
- Its development showed that PPP is a **viable** model for R&D for NTDs
- However, **access to this drug is limited**
  - ✓ even in a context where preferential pricing should apply
  - ✓ *de facto* monopoly of a drug as the **only quality-assured source**.
- Miltefosine availability affected by changes in ownership rights over the years
- Despite existing MoU, dependency on the goodwill of company (which changes)
- Not all NTDs can be tackled with big pharma donation
Lessons learned

- **PPP or PDP should not only target the registration of the product**
  - Improve mechanism(s) to enforce framework and legal agreements between partners
  - Access plan imperative

- **Transparency** in drug pricing structures

- **PRV as incentive to enhance R&D for NTD need fixing**
  - Applicants seek regulatory approval and demonstrate appropriate access strategies
  - Signs of change: **2017 PRV for benznidazole for Chagas diseases** (Chemo Group, DNDi, Mundo Sano)

- **Develop short-mid-long term strategies for Leish drugs:**
  - Consolidate coordination and approach through coalition e.g. WHO Working Group
  - Pooled procurement and establishment of common buffer stock
This project has received funding from the European Union's horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 642609.
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L infantum: ZOONOTIC
✓ Middle East/ Central Asia
✓ Mediterranean
✓ Latin-America

L donovani: ANTHROPONOTIC
✓ Indian subcontinent
✓ East Africa

Ninety percent of the global burden occurs in just six countries:
India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia

Countries reporting imported VL cases
Uganda - 93
Ethiopia - 73
Nepal - 16
France - 10
Greece - 6
Yemen - 5
Argentina - 3
Georgia - 3
Iraq - 3
Morocco - 2
Israel - 1
Jordan - 1
Russian Federation - 1
Saudi Arabia - 1
Thailand - 1

Number of new VL cases reported, 2015
Significance of access problems

Conceptual framework

Adoption
Global
National

Affordability
Government
NGOs

Availability
Quality
Pricing
Procurement
Distribution
Delivery

End user: acceptability
End user

ACCESS

HYPOTHESIS: ACCESS TO CARE IS INADEQUATE