The Visceral Leishmaniasis Global R&D and Access Initiative

J. Alvar & A. Heumber

Drugs for Neglected Diseases initiative
Summary

VL, a general overview of needs
  • Impact and progress made
  • From patient needs to public health perspective: PKDL, Contacts, Asymptomatic carriers

VL as WHO R&D demonstration project
  • Concept
  • Objectives
  • Guiding principles
Leishmaniasis

- VL & CL (MCL, DCL, PKDL, LR, HIV/VL)
- 98 endemic countries
- Incidence: 0.4 M VL, 1.2 M CL cases/yr
- 2.35 million DALYS

> 90% VL
> 90% CL
> 90% VL and/or CL

World map showing distribution of VL and CL with percentages and regions affected.
Challenges at the turn of the millennium

- Leishmaniasis sharing all characteristics of a typical poverty-related disease (NTD) PLUS
- Lack of up-dated information
- No visibility according to its burden
- Epidemiological complexity
- No concept on how to manage the disease
- No global strategy
- No political recognition
  - WHA Resolution 2007/60.13

Disease not under proper control
A productive decade for VL

- Gilead donates Ambisome
- Single dose Ambisome
- Price reduction Ambisome
- SSG/PM
- Miltefosine P-III
- Paromomycin Phase IV
- K-A Elimination Program
- WHA Resolution
- Expert Committee
- TRS 949
- London Declaration
- Country profile
- Gilead donates Ambisome

- AECID
- BMGF
- Sanofi
- EU
- Others

- DNDi started
- WHO/NTD started
- DNDi
- BMGF
- AECID
- EU
- Sanofi
- Others
Pitfalls in chemotherapy: the African case

<table>
<thead>
<tr>
<th>Drugs</th>
<th>SSG</th>
<th>Ampho B Liposomal</th>
<th>Ampho B deoxycholate</th>
<th>MIL</th>
<th>PM sulphate</th>
<th>SSG+PM</th>
<th>LAB+SSG</th>
<th>LAB+MIL</th>
<th>PM+MIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical efficacy</strong></td>
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<tr>
<td><strong>Asia</strong></td>
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<tr>
<td>35-95% (depending on areas)</td>
<td>&gt; 97% all regions</td>
<td>&gt; 97% single dose: &gt; 96%</td>
<td>94-97% (India)</td>
<td>94% (India)</td>
<td>Not documented</td>
<td>&gt; 97%</td>
<td>&gt; 97%</td>
<td>&gt; 97%</td>
<td></td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td>93%</td>
<td>Not fully established</td>
<td>72%</td>
<td>84%</td>
<td>91%</td>
<td>87%</td>
<td>79%</td>
<td>Not documented</td>
</tr>
<tr>
<td>33 - &gt;97% (depending on areas)</td>
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<tr>
<td><strong>Resistance</strong></td>
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<tr>
<td>As high as 60% (India)</td>
<td>Not documented</td>
<td>Not documented</td>
<td>20% (Nepal)</td>
<td>Lab isolates (easily)</td>
<td>Lab isolates (easily)</td>
<td>Lab isolates</td>
<td>Lab isolates</td>
<td>Lab isolates (easily)</td>
<td></td>
</tr>
</tbody>
</table>

Is it not the right time to approach therapy based in the parasite specifies?
Interlinked contexts with poorly described infection sources driving disease manifestation and outbreaks on top of a complex social, nutritional and immune picture.
# Post Kala-azar Dermal Leishmaniasis (PKDL)

An immune mediated process: VL (Th2) - PKDL (Th2/Th1) - cure (Th1)

## Main clinical differences

<table>
<thead>
<tr>
<th></th>
<th>Sudan</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common presentation</td>
<td>polymorphic, papular</td>
<td>monomorphomic, macular</td>
</tr>
<tr>
<td>Typical distribution (face-arms/chest/legs)</td>
<td>yes</td>
<td>often not</td>
</tr>
<tr>
<td>Spontaneous cure</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>May occur while on Rx for VL</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Genital lesions</td>
<td>uncommon</td>
<td>common</td>
</tr>
</tbody>
</table>
Hypothesis: PKDL patients do play a role in transmission

Objectives:
• To establish the burden of VL:PKDL at the village level
• To prove infectivity of PKDL patients according to forms
• Xenodiagnosis vs surrogate biomarker
• To provide recommendations for treatment, control, & surveillance
Recommendations by the Consortium on PKDL, 2013
Treatment & Pathogenesis

Africa: SSG 20 mg Sb\textsuperscript{5+}/kg IM/IV for 30–60 days
Asia: miltefosine, for 12 weeks daily 100 mg or 50 mg weighting ≥ 25 kg or <25 kg, respectively

\textbf{AmBisome:} 5 mg/kg per day IV, twice a week up to 30 mg/kg

- Pharmacokinetic of drugs targeting the skin
- Understand the pathogenesis by clinical forms and regions
- Randomized clinical trials of short course regimens
- Immuno-chemotherapy
Major emerging foci & Outbreaks (2006-13)

- **Tchad**: Sept 07, Teguine, 159 CL cases
- **Afghanistan**: Kabul, Mazir-i-Sharif, Others? 200,000 CL cases
- **Pakistan**: Singh, NWFP, Beluchistan, 2006, 25000 CL cases
- **Sri Lanka**: April 03, North-South, >1000 CL cases
- **Kenya**: August 06, Wajir, 40 VL cases
- **Ethiopia**: May 07, Somali region, 25 VL cases
- **Somalia**: Huddur, June 06, 263 VL (05), 329 (Jun-Ap 06)
- **Madrid**: 2010-12, Fuenlabrada, 254 VL, CL
- **Irak**: April 05, Baqubah, 250 CL cases
- **Georgia**: 2006-11, Tblisi, 600 VL cases
- **Paraguay**: 2008-11, Asunción, 500 VL cases
- **South Sudan**: 2009-12, Jonglei, 25,000 VL
Contacts: VL cluster transmission by year of onset, Bangladesh  
(Bern et al., 2005)

Should contacts be put under prophylaxis?
Detection of *Leishmania infantum* cryptic infection in asymptomatic blood donors living in an endemic area (Eivissa, Balearic Islands, Spain) by different diagnostic methods

C. Riera \(^a\), R. Fisa \(^a\), M. Udina \(^b\), M. Gállego \(^a\), M. Portus \(^a\)

Table 1  Results of the different diagnostic methods applied in 122 blood donors: sensitivity of the several techniques

<table>
<thead>
<tr>
<th>Blood donors</th>
<th>No. of blood donor positives/No. of blood donors studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studied</td>
<td>Serology: ELISA, WB</td>
</tr>
<tr>
<td>122</td>
<td>7/122, 14/122</td>
</tr>
<tr>
<td></td>
<td>Sensitivity of the technique(^b)</td>
</tr>
</tbody>
</table>

\(^a\) We consider as probably infected those donors that tested positive on at least one of the techniques assayed.

\(^b\) Sensitivity = no of donors positives/no of donors probably infected.

\(^c\) Sensitivity of DTH and BC culture tests was calculated on 30 donors considered as probably infected (30 of the 67 screened).
Asymptomatic Infection with Visceral Leishmaniasis in a Disease-Endemic Area in Bihar, India

Roshan K. Topno,* Vidya N. R. Das, Alok Ranjan, Krishna Pandey, Dharmender Singh, Nawin Kumar, Niyamat A. Siddiqui, Vijay P. Singh, Shreekant Kesari, Narendra Kumar, Sanjeev Bimal, Annadurai Jeya Kumar, Chetram Meena, Ranjeet Kumar, and Pradeep Das

### Table 2

Comparative results of rK-39, PCR, and DAT among screened population at baseline survey, Bihar, India*

<table>
<thead>
<tr>
<th></th>
<th>DAT</th>
<th>rK-39</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. positive</td>
<td>No. negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>8</td>
<td>305</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>8</td>
<td>308</td>
</tr>
</tbody>
</table>

*PCR = polymerase chain reaction; DAT = direct agglutination test.
Dogs Infectivity to *Phlebotomus perniciosus*

(Molina et al., 1994)

(Guarga et al., 2000)
Summary of main challenges

On going studies completed, bringing 1-3 new oral-combination treatments by 2018

African VL
  - Development of a therapy based in the parasite specifies

PKDL
  - Infectivity by clinical forms
  - Which PKDL patients need treatment, for how long

Contacts
  - Development of an (oral) drug to protect family members

Asymptomatic carriers
  - Infectivity
  - Development of an oral drug as preventive chemotherapy for MDA

DNDi is committed to move from drug development for treating individual patients to become aligned with the London Declaration contributing in the control/elimination of VL by 2020
...in the new landscape London-2020

Patients and implementation first...
  … but fully committed in (de-)figthing leishmaniasis by:

- **Up stream research**
  - Oxaboroles, 2098
- **Down stream research**
  - Fexi/miltefosine
- **Innovation**
  - Open spaces, new areas
- **Implementation**
  - Engaging with MoHs

Gracias
Identification of Health R&D Demonstration Projects

The demonstration projects

These projects should aim at developing health technologies (medicines, diagnostics, medical devices, vaccines, etc.) for diseases that disproportionately affect developing countries and for which identified R&D gaps remain unaddressed due to market failures. The projects must demonstrate effectiveness of alternative, innovative and sustainable financing and coordination approaches to address identified R&D gaps.

- **The Visceral Leishmaniasis (VL) Global R&D & Access Initiative** - Drugs for Neglected Diseases initiative (DNDi), submitted via AFRO and EMRO.
- **Exploiting the Pathogen Box: an international open source collaboration to accelerate drug development in addressing diseases of poverty** – Medicines for Malaria Venture (MMV), submitted via EURO.
- **Development of Class D Cpg Odn (D35) as an Adjunct to Chemotherapy for Cutaneous Leishmaniasis and Post Kala-Azar Dermal Leishmaniasis (Pkdl)** - United States Food and Drug Administration (US FDA), et al., submitted via AMRO.
- **Development for Easy to Use and Affordable Biomarkers as Diagnostics for Types II and III Diseases** - African Network for Drugs and Diagnostics Innovation (ANDI), et al., submitted via AFRO.
Visceral Leishmaniasis Demonstration Project - WHO

- DNDi VL Global Research & Access Initiative, selected by EMRO, AFRO and initially supported by Sudan, France, Switzerland, Spain

- Demonstrate that Health R&D can be boosted through:
  a) collaborative cross-regional coordination,
  b) innovative and sustainable approaches for R&D (open innovation and IP management),
  c) innovative sustainable financing mechanisms (i.e. pool funding)

- Guiding principles/CEWG: Sharing knowledge and open innovation; Equitable access; Sustainable funding; Exploring innovative incentives mechanisms; Coordination through collaborative approach.
Demonstration Project – WHO process

- 5-year project; Budget: 35 M €
- Research, clinical trials and access in 4 continents: cross-regional operationnal activities through collaborative coordination
- **Multiples partners:** MoH, Research Institutes, WHO, pharmaceutical partners etc.
- **Political and financial involvement of countries** (endemic countries, traditional and new donors countries); Looking at **Pool funding mechanism**.
- **Next steps:** Implementation.
- Report to the WHA on initial outcomes;
- **Global debate on sustainable financing and coordinating framework.**
**Objective 1:** Development 1st line treatment for East Africa, Latin America, 2nd line for Indian sub-continent.

Activity 1: Identification of new compounds from lead optimization to preclinical phase.

Activity 2: Moving an NCE from pre-clinical phase to POC (VL2098).

Activity 3: Completing clinical development of existing candidates up to registration (Fexinidazole).

**Objective 2:** Xenodiagnosis and qPCR.

**Objective 3:** Research on skin penetration of existing drugs.

**Objective 4:** Building up a data sharing platform to monitor the development of resistance to existing treatments.

**Incentives:**
- Open source, Drug Booster
- De-linkage, Grant with access clauses
- Bilateral agreements with donors
- De-linkage, Capacity building, Collaborative coordination, Regulatory pathways
- Xeno: Capacity building, transfert techno., Data sharing, qPCR: De-linkage, Prize
- Open source, data sharing

**Mechanisms:**
- Pool funding
- IMI/EU
- EDCTP, IMI/EU
- EDCTP, donors
- EDCTP/EU, donors

**Partners:**
- Pharmaceutical partners, OSSID/CDRI, Dundee/GSK consortium
- Pharmaceutical partners, CDRI, LSHTM, TB Alliance, University Auckland
- LEAP, PATH, ICCDRB
- LEAP, KEMRI, Fiocruz Institute, ICMR, Institute of Endemic Disease, Sudan MoH, LSHTM, Pharma partners
- University Utrecht, Institute of Endemic Diseases, Caracas Univ, Ferrer Group, tiefel GSK, Salpêtrière Hospital, SGS
- WWARN, MoHs, ITM-Antwerp
Objective 1: To develop new safe and effective oral treatments as monotherapy and as early as possible as combination treatment (medical product) to prevent the risk of resistance development and a very safe, short-course one for asymptomatic careers once their role in disease transmission has been better established.

Objective 2: To develop technology of diagnostic (xenodiagnoses coupled with a quantitative PCR) in order to evaluate the role in transmission of asymptomatic careers and PKDL patients.

Objective 3: To develop a treatment for Post-kala-azar dermal leishmaniasis (PKDL) (medical product).

Objective 4: To support development of a shared, open-access data base to identify determinants of treatment effectiveness.
Guiding principles of the Initiative:

- **Sharing knowledge and open innovation:** The establishment of a Drug Booster Consortium as an open knowledge platform would be a key asset to speed up upstream research, avoid duplication of research and decrease cost of R&D. Partners within the Drug Booster would agree to screen their libraries together, increasing the chance to identify hits for later optimization.

- **Exploring innovative incentives mechanisms:** The Initiative would explore innovative mechanisms such as a milestone prize for xenodiagnoses and quantitative PCR.

- **Equitable access:** To ensure affordable access, the Initiative would emulate collaboration with industrial partners similar to that between DNDi and Sanofi for fexinidazole, a new drug being tested against the disease. Such agreements would make available, as public goods, any new therapeutic and diagnostic tools developed, as well as making them available at affordable prices.
Visceral Leishmaniasis Demonstration Project – Guiding principles

- **Sustainable funding:**
  a) New funding mechanisms, **such as a pool funding**;
  b) **The European and Developing Countries Clinical Trials Partnership (EDCTP 2)**
  c) **Innovative Medicines Initiative (IMI)**
  d) contributions from **emerging-economy countries** and regions affected by the disease (Brazil, India, Middle East and North Africa)
  e) **prizes**.

- **Coordination through cross regional collaborative approach:**
  The VL Global R&D & Access Initiative would be set-up in partnership with the existing VL consortia and research platforms from the different relevant regions.
Next steps: towards implementation & demonstration

WHO process: pilot innovative mechanisms to finance and coordinate Health R&D; Induces transparency (cost etc).

Need on-going political and funding support from MSs from all regions: AFRO, SEARO, EMRO, EURO, PAHO, WPRO

Coordination and partnerships with partners for the implementation: LEAP, KEMRI, pharma, Academics, MoHs, etc.

Outcome of WHO Stakeholders’ meeting in Geneva
Project plan and funded budget
Report to MSs at next WHAs on mid-term outcomes
Link with parallel debate on CEWG Follow-up: Financing and Coordination and Health R&D Observatory
THANK YOU
Hypothetical model of the natural history of infection & disease in leishmaniasis

CONDITION | IFAT | rK39 | PCR | Culture | CPA | LST | IFNγ | Infectivity
---|---|---|---|---|---|---|---|---
Infected | + | - | +/- | - | + | + | + | + | ?
Prepatent | ++ | + | ++ | + | - | - | - | - | ?
Asympt. carrier – Infectious | + | + | + | +/- | + | + | + | ?
Asympt. - Protected | +/- | - | +/- | - | ++ | ++ | ++ | ?
Cured (after TX) | + | +/- | - | - | ++ | ++ | ++ | -
Aims of the VL Program…

- **In the Near Term**
  - Register combinations for East Africa
  - Provide ammunition for policy change in India and LatAm
  - Determine suitability of miltefosine as an oral combination partner in East Africa

- **Longer Term**
  - Develop new oral drugs as quickly as possible by
    - New PoC paradigm
    - Increasing sites and recruitment rates
  - Upgrade LEAP to v2.0
  - Determine role of asymptomatics & PKDL patients as disease reservoir
  - Increase Discovery pipeline