A global approach to combat Visceral Leishmaniasis

J. Alvar

Drugs for Neglected Diseases initiative

EDCTP, Berlin 30 June 2014
Outline

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
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
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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td>35-95%</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>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td>93%</td>
<td>33 - &gt;97% (depending on areas)</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><strong>Resistance</strong></td>
<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 (easily)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Cure (efficacy) at end of treatment and at 6 months after treatment.

<table>
<thead>
<tr>
<th></th>
<th>SSG</th>
<th>PM</th>
<th>$P^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Um el Kher, Sudan</td>
<td>14/17 (82.4%)</td>
<td>4/28 (14.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>· Kassab, Sudan</td>
<td>14/15 (93.3%)</td>
<td>7/15 (46.7%)</td>
<td>0.014</td>
</tr>
<tr>
<td>· Kenya</td>
<td>15/15 (100.0%)</td>
<td>12/15 (80.0%)</td>
<td>0.224</td>
</tr>
<tr>
<td>· Gondar, Ethiopia</td>
<td>37/40 (92.5%)</td>
<td>30/40 (75.0%)</td>
<td>0.066</td>
</tr>
<tr>
<td>· Arba Minch, Ethiopia</td>
<td>27/29 (93.1%)</td>
<td>28/29 (96.6%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Hailu PLoS NTD 2010

Gelenew PLoS NTD 2010
VL, elements fuelling transmission

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>monomorph, 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>

Zijlstra et al., Lancet ID, 2003
**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$^{5+}$/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
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, Beluschistan
  - 2006
  - 25000 CL cases

- Sri Lanka
  - April 03
  - North-South
  - >1000 CL cases

- Kenya
  - August 06
  - Wajir
  - 40 VL cases

- Ethiopia
  - May 06
  - Libo & Fogera
  - 2500 VL cases
  - Somali region
  - 25 VL cases

- Paraguay
  - 2008-11
  - Asunción
  - 500 VL cases

- Georgia
  - 2006-11
  - Tblisi
  - 600 VL cases

- Irak
  - April 05
  - Baqubah
  - 250 CL cases

- South Sudan
  - 2009-12
  - Jonglei
  - 25,000 VL

- Madrid
  - 2010-12
  - Fuenlabrada
  - 254 VL, CL

- Somalia
  - Huddur
  - June 06
  - 25 VL cases
  - 263 VL (05)
  - 329 (Jun-Ap 06)

- Pakistan
  - Singh, NWFP, Beluschistan
  - 2006
  - 25000 CL cases

- Sri Lanka
  - April 03
  - North-South
  - >1000 CL cases

- Somalia
  - Huddur
  - June 06
  - 263 VL (05)
  - 329 (Jun-Ap 06)
Contacts: VL cluster transmission by year of onset, Bangladesh (Bern et al., 2005)

Should contacts be put under prophylaxis?
Asymptomatic infections

Importance

- 1:4 Kenya, Uganda 1:8, Spain 1:50
- Blood donors (Riera et al, TRSMH, 2004)
- Serological/PCR surveys (Topno et al, AJTMH, 2010):
  - From 21 sero +  17 were PCR +
  - From 313 sero -  2,5% were PCR +

Role of Infective asymptomatic dogs  (Molina et al., TRSTMH, 1994)

Definition

- Serology
- PCR
- LST
- Cytokine environment

Are asymptomatic human carriers playing a role in transmission?
Summary of main challenges

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

African VL
  - Develop Rx based in the parasite specifies
PKDL
  - Infectivity by clinical forms
  - Which PKDL patients need Rx, which Rx?
Contacts
  - Develop (oral) drug to protect family members
Asymptomatic carriers
  - Infectivity
  - Develop 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:

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

Gracias
Back up slides
### VL reported cases (average 2004-08) and estimates

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases reported/year</th>
<th>Estimated annual</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>3,661</td>
<td>5,000 to 7,000</td>
</tr>
<tr>
<td>West Africa</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>East Africa</td>
<td>8,569</td>
<td>30,000 to 40,000</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>875</td>
<td>1,500 to 2,000</td>
</tr>
<tr>
<td>Middle East &amp; Central Asia</td>
<td>2,496</td>
<td>5,000 to 7,500</td>
</tr>
<tr>
<td>Indian Subcontinent</td>
<td>42,619</td>
<td>160,000 to 320,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>58,220</strong></td>
<td><strong>201,500 to 376,500</strong></td>
</tr>
</tbody>
</table>

Alvar et al., PLoS One, 2012
Hypothetical model of the natural history of infection & disease in leishmaniasis

**CONDITION** | **IFAT** | **rK39** | **PCR** | **Culture** | **CPA** | **LST** | **IFNg** | **Infectivity**
---|---|---|---|---|---|---|---|---
Infected | + | - | +/- | - | + | + | + | ?
Prepatent | ++ | + | ++ | + | - | - | - | ?
Asymp. carrier – Infectious | + | + | + | +/- | + | + | + | ?
Asymp. - 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
Challenges at the turn of the millenium

- 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
- Paromomycin Phase IV
- K-A Elimination Program
- WHA Resolution
- DNDi started
- WHO/NTD started
- DNDi
- BMGF
- Sanofi
- EU
- Others
# DNDi’s VL portfolio

<table>
<thead>
<tr>
<th>Region</th>
<th>Product</th>
<th>Status</th>
<th>Phase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Leap 0106</td>
<td>AmBisome</td>
<td>completed</td>
<td>Recommen. &amp; Public.</td>
</tr>
<tr>
<td></td>
<td>Leap 0208</td>
<td>Combo</td>
<td>Phase II</td>
<td>Last patient</td>
</tr>
<tr>
<td></td>
<td>Leap 0511</td>
<td>HIV/VL</td>
<td>Ph-III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sudan</td>
<td>Fexi</td>
<td>Ph-II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSG/PM PV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>Bangladesh</td>
<td>Combo/LAB x 5</td>
<td>completed</td>
<td>Public &amp; Recomm.</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>feasibility/implement. Combo &amp; LABx1 &amp;LABx3</td>
<td>Ph-IV</td>
<td></td>
</tr>
<tr>
<td>America</td>
<td>Brazil</td>
<td>Combo &amp; LAB</td>
<td>Ph-II</td>
<td></td>
</tr>
</tbody>
</table>
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></td>
<td>Serology</td>
</tr>
<tr>
<td></td>
<td>ELISA</td>
</tr>
<tr>
<td>Total studied</td>
<td>7/122</td>
</tr>
<tr>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Infected a</td>
<td>36</td>
</tr>
<tr>
<td>Sensitivity of the technique b</td>
<td>7/36</td>
</tr>
<tr>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>Culture</td>
<td>PBMC</td>
</tr>
<tr>
<td></td>
<td>0/67</td>
</tr>
<tr>
<td>Sensitivity of DTH and BC culture tests was calculated on 30 donors considered as probably infected (30 of the 67 screened).</td>
<td></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>DAT</th>
<th>rK-39</th>
<th>PCR</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. positive</td>
<td>No. negative</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>4</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>15</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>19</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>305</td>
<td>313</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>308</td>
<td>316</td>
<td></td>
<td></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)
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
- Multiple 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.
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.
VL demonstration project
Funding & Incentives mechanisms & Partners
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
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.
Demonstrate that Health R&D can be boosted through:

- a) collaborative cross-regional coordination,
- b) innovative & sustainable approaches for R&D (i.e: drug accelerator)
- c) innovative sustainable financing mechanisms (i.e: pool funding)

Guiding principles/CEWG: Sharing knowledge; Equitable access; Sustainable funding; Exploring innovative incentives mechanisms
Objective 1: To develop new safe and effective oral treatments as monotherapy and as early as possible as combination treatment and a very safe, short-course one for contacts and asymptomatic careers once their role in transmission has been 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 PKDL (medical product).

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