"Are there any game-changing tools in the development pipeline for kala-azar?"

**SPEAK India II meeting**
23-24 April, 2018,
New Delhi

Dr Suman Rijal, MBBS, MRCP (UK), FRCP, PhD
Director,
Drugs for Neglected Diseases *initiative*, India
Background

• Even after kala-azar elimination is reached:
  - thousands of cases will continue to occur
  - the possibility of major new outbreaks remain
  - There will be new foci reporting cases
• Proportion of kala-azar amongst suspect kala-azar case decreasing.
• Limitations of the current diagnostic tests: relapsed VL, assess cure and PKDL
• Need for more appropriate treatment regimens: PKDL, HIV-VL
• Challenges for the current parenteral treatment of KZ in the programme:
  - number of cases per treatment site decreasing
  - continued need for training, logistics support, and monitoring
• Is the current treatments suitable in the maintenance phase and beyond. asymptomatic leishmanial infection ?
**Diagnostics to sustain & monitor VL elimination (2018-2023?)**

- **Context:** Low prevalence of VL cases. PKDL are more relevant. **Need to diagnose and treat all VL and PKDL cases promptly (and effectively).**

<table>
<thead>
<tr>
<th>NEED</th>
<th>CURRENT METHODS</th>
<th>GAP</th>
<th>POTENTIAL SOLUTIONS</th>
</tr>
</thead>
</table>
| Diagnose all VL cases                     | Clinical signs + rk39 RDT               | Possible if performance of rk39 RDT decreases with low prevalence  | • RDT that can detect cases earlier (< 2 weeks fever) with high NPV and PPV (Ag-detection?)  
• Non-invasive confirmatory test to include in an algorithm (NAAT?)                                                                                       |
| Diagnose all PKDL cases                   | Clinical signs + rk39 RDT / microscopy or NAAT to confirm | Yes                                                                 | • Easy to use NAAT (LAMP?)  
• Ag-detection RDT to be used in skin samples                                                                                                             |
| Monitor treatment success (VL and PKDL)   | Clinical evaluation, microscopy         | Yes                                                                 | • IgG1 RDT (to be further evaluated)  
• Easy to use NAAT (LAMP)  
• Immunological markers                                                                                                                                      |

*Information courtesy of: FIND*
# Diagnostics to sustain & monitor VL elimination – Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Feasibility</th>
<th>Development</th>
<th>Evaluation</th>
<th>Demonstration (registered)</th>
<th>Scale-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VL</strong></td>
<td>• Leishmaniasis-RDT (Ag detection)</td>
<td></td>
<td>• Leishmania Antigen Detect ELISA (Inbios)</td>
<td>• Loopamp Leishmania Detection Kit (NAAT)</td>
<td></td>
</tr>
<tr>
<td>PKDL</td>
<td></td>
<td></td>
<td>• VL ELISA (Ag detection – Kalon)</td>
<td>• STAT-NAT Leishmania (NAAT)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td>• KAtex(Ag detection – Kalon)</td>
<td></td>
</tr>
<tr>
<td>monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leishmaniasis IgG1-RDT (Ab-detection; Coris)</td>
<td></td>
<td>• Loopamp Leishmania Detection Kit (NAAT; Eiken)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Leishmania Antigen Detect ELISA (Inbios)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• VL ELISA (Ag detection – Kalon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Information courtesy of: FIND
New treatment regimens in PKDL

- **L-AMB 30 mg/kg over 3 weeks**: Six cases of confirmed and one presumed case of clinical rhabdomyolysis post-PKDL treatment were diagnosed over a period of 3 months (Marking et al. 2014 *PLOS NTD*)

- **L-AMB 15 mg/kg, given over 15 days**: 273 patients assessed at 12 months (den Boer et al. 2018 CID)
  - All patients completed treatment without severe or serious adverse events
  - Complete or major improvement of lesions: 245 (89.7%) patients;
  - Completely cured: 213 (78.0%)
  - Lesions did not improve: 28 (10.3%)
  - New lesions appeared: 13 (4.8%)

- **Ongoing CT (Started Q4 2017)**: To measure the safety and efficacy in the Indian Sub Continent:
  - L-AMB monotherapy regimen (total dose of 20 mg/kg)
  - L-AMB (total dose of 20 mg/kg) in combination with miltefosine daily for three weeks (allometric dosing)
## Discovery/preclinical portfolio: March 2018

<table>
<thead>
<tr>
<th>Stage / Disease</th>
<th>Screening</th>
<th>Hit-to-lead</th>
<th>Lead optimization</th>
<th>Pre-clinical</th>
<th>Phase I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmaniasis</td>
<td>Commercial libraries</td>
<td>THQ series, Sulphonamide series (LOLA), Indoles (LOLA), Ureas (LOLA), 1x Daiichi-Sankyo series</td>
<td>CC1 series, 205 series, 448 series, CF series, Azetidine series (Broad), CytB series</td>
<td>CPG D35, DNDI-5561, GSK-3186899 / DDD853651, GSK-3494245 / DDD1305143</td>
<td>DNDI-6148, DNDI-0690</td>
</tr>
</tbody>
</table>

**Key:**
- **DNDI project**
- **Partnered project**
- **External project**

**Pharma libraries & NPs:**
- THQ series
- Booster HS05
- Sulfone (Sanofi)

**Series:**
- 6 x Booster series
- Booster HS05
- Sulfone (Sanofi)
Project timelines

**HIV-VL India (MSF)**
- Phase III: 12 mo
- Phase III CSR

**PKDL extension India**
- CSR

**PKDL India**
- Phase III: 16 mo
- Phase III CSR

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-VL India (MSF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKDL extension India</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKDL India</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NCEs, simplified plan**
- Phase I studies
- DDI
- PoC
- Phase IIb/III

Legend:
- HV study
- HV study (follow-up period)
- Patient study (recruitment period)
- Patient study (follow-up period)
- Set-up / regulatory approvals
- Major milestone
Limitations of VL diagnostic algorithms

- Develop diagnostic guidance tools
- Persistent fever syndrome (≥ 7 days)

Kala-azar suspect: fever ≥ 2 wks + splenomegaly, LN or wasting

Diagnostic algorithm focusing only on VL

Direct Agglutination Test (DAT)

Tissue aspirate

Treatment for kala-azar
Persistent fever

- Rickettsiosis
- Scrub typhus
- Leptospirosis
- UTI
- Pneumonia
- Pharyngitis
- RTI

- VL
- TB
- Enteric fever
- Borreliosis
- Cancer
- Others
- Undefined

Diagnostic panorama (BPKIHS, Nepal)
Pre-test probabilities (BPKIHS)

- Rickettsiosis 13%
- Scrub typhus 4%
- Leptospirosis 5%
- UTI 7%
- Pneumonia 3%
- Pharyngitis 2%
- TB 5%
- Enteric fever 2%
- Borreliosis 1%
- Cancer 1%
- Others 6%
- RTI 1%
- Undefined 1%
Diagnostic guidance (Nepal)

- **Kala Azar (VL)**
  - RDT +
  - BM +
  - Splenomegaly
  - HB <10
  - Fever ≥ 30 days
  - RDT -
  - BM -

- **Tuberculosis**
  - AFB +
  - GenXpert +
  - Abnormal chest X-ray
  - Fever ≥ 30 days
  - GenXpert -

- **Scrub typhus**
  - Skin eschar +

- **Rickettsiosis**

- **Leptospirosis**

- **Fever ≥ 7 days**

- **Pneumonia**
  - Abnormal chest x-ray
  - Abnormal lung auscultation
  - Normal chest x-ray

- **Enteric fever**
  - Blood culture +
  - Abdominal tenderness

- **Acute Leukaemia**
  - ↑ Blasts in blood smear or BM
  - ↑↑ WBC
  - Normal WBC

- **Intra-abdominal infections**
  - Liver abscess/Choledolithiasis/Appendicitis
  - Abnormal US
  - Abdominal tenderness
  - Normal US

- **Meningitis**
  - Abnormal CSF
  - Meningeal signs
  - Normal CSF

- **Urinary tract infection**
  - Urine culture +
  - Urine analysis +

  - Urine culture -
  - Urine analysis -

Font size and intensity correlate with positive / negative likelihood ratio.

Arguments in favour of diagnosis

Arguments against diagnosis
WHO demonstration project: multiplexed point of care test for acute febrile illness (mPOCT): under development at THSTI.
Conclusions

• Current gaps and need for new tools in VL elimination has been well defined. Emphasis also needs to be for the post elimination period.

• Several diagnostic tests are in different stages of development - Completion of evaluation, validation and registration is recommended. Multi-country validation studies needed.

• Integration of diagnosis for persistent fever syndrome is probably the way forward. Development of multiplexed diagnostics and validation of diagnostic guidance is needed.

• Opportunities for NCE leading to new oral treatments for leishmaniasis are very optimistic.

• SPEAK consortium should support and advocate for continued R&D efforts for better tools.
Thank you