AfriKADIA – WP2 diagnostics

Isra Cruz, FIND

25th LEAP Platform Meeting, Kampala Uganda. 3-4 October 2018
Aim: To evaluate less invasive tools for diagnosis, prognosis and monitoring treatment of VL in clinical trials in eastern Africa

Objectives:
To demonstrate the utility of less invasive diagnostic tools for managing and monitoring VL cases.

• Evaluate LAMP and different biomarkers as tests-of-cure and predictors of relapses to replace the current invasive methods.

• Evaluate a new RDT for diagnosis of primary case detection, either in passive or in active case detection.
Solutions proposed

By 2020:

RDT (rK28, IgG1) – Improve VL diagnostic algorithm (Screening Study)

Improve test of cure/treatment monitoring in clinical trials and patient’s management (test-of-cure/treatment monitoring study)

LAMP, IgG1 ELISA

LPA, CRA
**Coordination: FIND**

<table>
<thead>
<tr>
<th>Screening LEAP-DNDi treatment Centres</th>
<th>Kenya</th>
<th>Kimalel</th>
<th>TASKS</th>
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<tbody>
<tr>
<td></td>
<td>Kacheliba</td>
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<td>Evaluate rK39 and rK28 RDTs</td>
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<td></td>
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<td>FIND, IEND, KEMRI, MUniv, GUniv, AMC, DNDi</td>
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<td>Uganda</td>
<td>Amudat</td>
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<td>Evaluate the anti-\textit{Leishmania} IgG1 RDT</td>
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<td>LSHTM, IEND, KEMRI, MUniv, GUniv, AMC, DNDi, FIND</td>
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<td>Sudan</td>
<td>Doka</td>
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<td>Evaluate \textit{Leishmania} Detection Kit</td>
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<td>Loopamp\textsuperscript{TM}, IEND, UGondar, AMC, FIND</td>
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<td>Ethiopia</td>
<td>Gondar</td>
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<td>Evaluate the anti-\textit{Leishmania} IgG1 RDT (and qELISA)</td>
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<td>LSHTM, IEND, UGondar, DNDi, FIND</td>
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<td>Evaluate \textit{Leishmania}-specific lymphoproliferative response and cytokine expression after whole blood stimulation assay</td>
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<td>ISCIII, IEND, UGondar, DNDi, FIND</td>
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**Crosscutting QC/QA (WP1-WP3): Coordinated by AMC**
• Laboratory confirmation rate of VL in eastern Africa is low (or no data) (WHO, 2016)

• Serology (rK39, DAT) is the main approach for VL diagnosis
  o Serology has limited performance in HIV+ patients, and rK39 has reduced sensitivity in eastern Africa

• Seronegative suspected patients (relapsed and previous VL too) are referred for microscopy of tissue aspirate
The diagnostic accuracy of rK39-based tests in eastern Africa is unsatisfactory.

- Boelaert *et al.*, Cochrane Database Syst Rev. 2014
  - 18 studies, 3622 participants
  - Chappuis *et al.*, BMJ 2006
  - WHO/TDR 2011. Diagnostics evaluation Series No.4

**IT-Leish rK39** RDT is the one recommended in eastern Africa.
Evaluation of new RDTs (rK28)

- Design of the k28 gene (IDRI, Pattabhi et al., PLoS NTDs 2010)

- Feasibility studies with different prototype RDTs
  - non-prospective
  - serum/plasma
  - parasitologically-confirmed VL cases
  - characterized controls
  - most don’t compare with IT-Leish
  - promising sensitivity, variable specificity
  - prototype from CTK Biotech is best candidate
Prospective evaluations of rK28 (CTK Biotech) in Sudan

- Not comparing with IT-LEISH

<table>
<thead>
<tr>
<th>Serum SE</th>
<th>Serum SP</th>
<th>Blood SE</th>
<th>Blood SP</th>
<th>Reference</th>
<th>Sample</th>
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<tbody>
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<td>94.5</td>
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<td>92.5</td>
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<td>Mukhtar 2005 AJTMH</td>
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<td>92.2</td>
<td>98.7</td>
<td>89.8</td>
<td>100</td>
<td>LNA m + DAT</td>
<td>Mukhtar 2005 AJTMH</td>
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<td>98.8</td>
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<td>-</td>
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<td>LNA micros.</td>
<td>Mukhtar 2018 PLoSNTD</td>
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Prospective evaluations of rK28 (CTK Biotech) in other countries

- Comparing with IT-LEISH

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>N° suspects</th>
<th>Reference</th>
<th>Blood</th>
<th>Serum/plasma</th>
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<td>rK28 (CTK)</td>
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<td>rK39 IT Leish</td>
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<td>rK39 Kalazar Detect</td>
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<td>SE</td>
<td>SP</td>
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<td>South Sudan</td>
<td>WHO</td>
<td>N=168</td>
<td>VL DX alg.</td>
<td>65.5</td>
<td>96.3</td>
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<tr>
<td>Kenya</td>
<td>KEMRI-FIND</td>
<td>N=113</td>
<td>VL DX alg.</td>
<td>83.7</td>
<td>100</td>
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</table>
• Microscopy is used in the diagnosis of relapses, inclusion of patients in clinical trials and also as ToC
  o Variable sensitivity, invasive, risky
  o Difficult to harmonize pre- and post-treatment sample (can be a challenge in CT)

• In Africa (...), the efficacy of the best therapeutic option is ~ 90% (Alvest et al., CMR 2018)
ToC/TM study

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<tr>
<th>DNA detection</th>
<th>Humoral immune response</th>
<th>Cell-mediated immune response</th>
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<tr>
<td>LAMP</td>
<td>IgG1 RDT /ELISA</td>
<td>Lymphoproliferation assay (CPA), Cytokine release assay (CRA)</td>
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Highly sensitive in VL diagnosis. Marker of parasite clearance (=PCR, qPCR)

Increased IgG1-specific responses are associated with relapse, whereas negativisation is associated with cure.

Both previously used to assess cure and relapses (incl. HIV/VL). Specific LP shows cure/protection. IFN-γ, IL-2, IP-10 and MIG cytokine levels increase after successful treatment, whereas IL-27 decreases.

Harmonization with ongoing activities by other partners and other EDCTP project
Interaction with other WPs

**WP1**

LEAP-DNDi sites
- Uganda
- Kenya
- Sudan
- Ethiopia

**Suspect VL case**

**VL case**

**MIL/PM Phase III trial (PK/PD)**

- Cure
- Relapse
- Rescue

**Screening phase**
- [rK39, DAT, microscopy]
- rK28, IgG1

**Treatment monitoring /ToC**
- [microscopy, qPCR]
  - LAMP, IgG1 (RDT, ELISA), WBA (CRA, LPA)

**WP2**

**WP3 (QC/QA)**
Improving access to VL diagnosis, Kenya

- Collaboration with MoHs, WHO and DNDi.
- Turkana, Wajir, Marsabit, Isiolo.
- Characterization and mapping of health facilities.
- Network of RDT and DAT centres.
- Capacity building:
  - VL diagnostic algorithm
  - RDT, DAT, microscopy
  - TOTs and cascade training
- Advocacy.

- Scenario to run (in collaboration with KEMRI and MoHs) an evaluation of rK28 at the health facility level
Thank you!

AfriKADIA

www.afrikadia.org