AfriKADIA – WP2 diagnostics

Isra Cruz, FIND

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AfriKADIA, WP2

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)

COMMUNITY HEALTH WORKER | HEALTH POST | MICROSCOPY CENTER | DISTRICT HOSPITAL | REFERENCE CENTRE

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

- LAMP, IgG1 ELISA
- LPA, CRA

Structure

AfriKADIA

Coordination: FIND				
Screening LEAP-DNDi treatment Centres	**Kenya**	Kimalel	TASKS	**Evaluate rK39 and rK28 RDTs** **FIND**, IEND, KEMRI, MUniv, GUniv, AMC, DNDi
		Kacheliba		
	Uganda	Amudat		
	Sudan	Doka		**Evaluate the anti-*Leishmania* IgG1 RDT** **LSHTM**, IEND, KEMRI, MUniv, GUniv, AMC, DNDi, FIND
		Um El Kher		
	Ethiopia	Gondar		

ToC/TM LEAP-DNDi treatment Centres	**Sudan**	Doka	TASKS	**Evaluate Loopamp™ *Leishmania* Detection Kit** **IEND**, UGondar, AMC, FIND
	Ethiopia	Gondar		**Evaluate the anti-*Leishmania* IgG1 RDT (and qELISA)** **LSHTM**, IEND, UGondar, DNDi, FIND
				Evaluate *Leishmania*-specific lymphoproliferative response and cytokine expression after whole blood stimulation assay **ISCIII**, IEND, UGondar, DNDi, FIND

Crosscutting QC/QA (WP1-WP3): Coordinated by AMC

Screening study, rationale

- 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
  - 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

Performance of VL RDTs

The diagnostic accuracy of **rK39**-based tests in **eastern Africa is <u>unsatisfactory</u>**

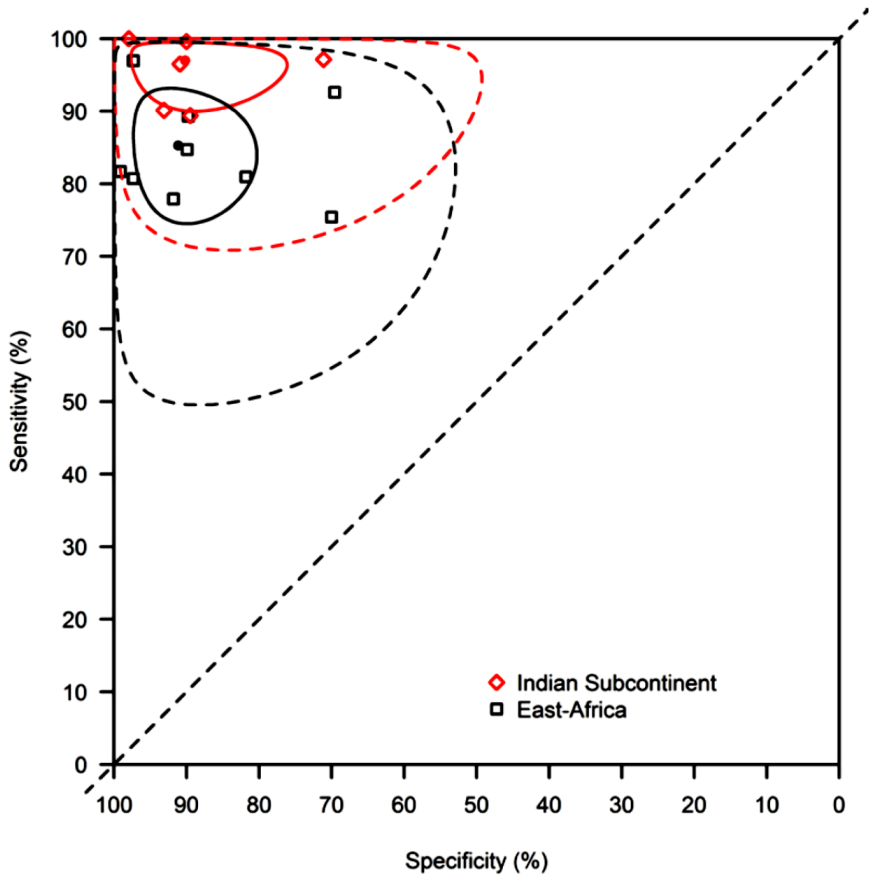
Boelaert *et al.*, Cochrane Database Syst Rev. 2014

- 18 studies, 3622 participants

- Chappuis *et al.,* BMJ 2006
- WHO/TDR 2011. Diagnostics evaluation Serties No.4

IT-Leish rK39 RDT is the one recommended in eastern Africa

Figure 8. rK39 ICT: summary of the meta-regression model with effects for geographic region using the bivariate normal model with a complementary log-log link function. The sensitivity was significantly lower in East Africa (85.3%; 95% confidence interval: 74.5 to 93.2) than in the Indian subcontinent (97.0%; 95% confidence interval: 90.0 to 99.5). There was no significant difference in specificity: the specificity (95% confidence interval) in East Africa was 91.1% (80.3 to 97.3) and in the Indian subcontinent 90.2% (76.1 to 97.7). The confidence region is indicated with a full line, the prediction region with a dotted line.



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

Evaluation of new RDTs (rK28)

- **Prospective evaluations of rK28 (CTK Biotech) in Sudan**
  - Not comparing with IT-LEISH

Serum		Blood		Reference	Sample	
SE	SP	SE	SP			
94.5	97.6	92.5	100	LNA micros.	285 VL suspects	Mukhtar 2005 AJTMH
92.2	98.7	89.8	100	LNA m + DAT	285 VL suspects	Mukhtar 2005 AJTMH
98.8	100	-	-	LNA micros.	185 VL suspects	Mukhtar 2018 PLoSNTD

Evaluation of new RDTs (rK28)

- **Prospective evaluations of rK28 (CTK Biotech) in other countries**
  - Comparing with IT-LEISH

Country Study N° suspects Reference	Blood						Serum/plasma					
	rK28 (CTK)		rK39 IT Leish		rK39 Kalazar Detect		rK28 (CTK)		rK39 IT Leish		rK39 Kalazar Detect	
	SE	SP	SE	SP	SE	SP	SE	SP	SE	SP	SE	SP
South Sudan WHO N=168 VL DX alg.	65.5	96.3	71.6	100	63.2	100	78.8	93.6	79.1	100	65.1	100
Kenya KEMRI-FIND N=113 VL DX alg.	83.7	100	82.6	100	-	-	91.3	100	85.5	100	-	-

ToC/TM study, rationale

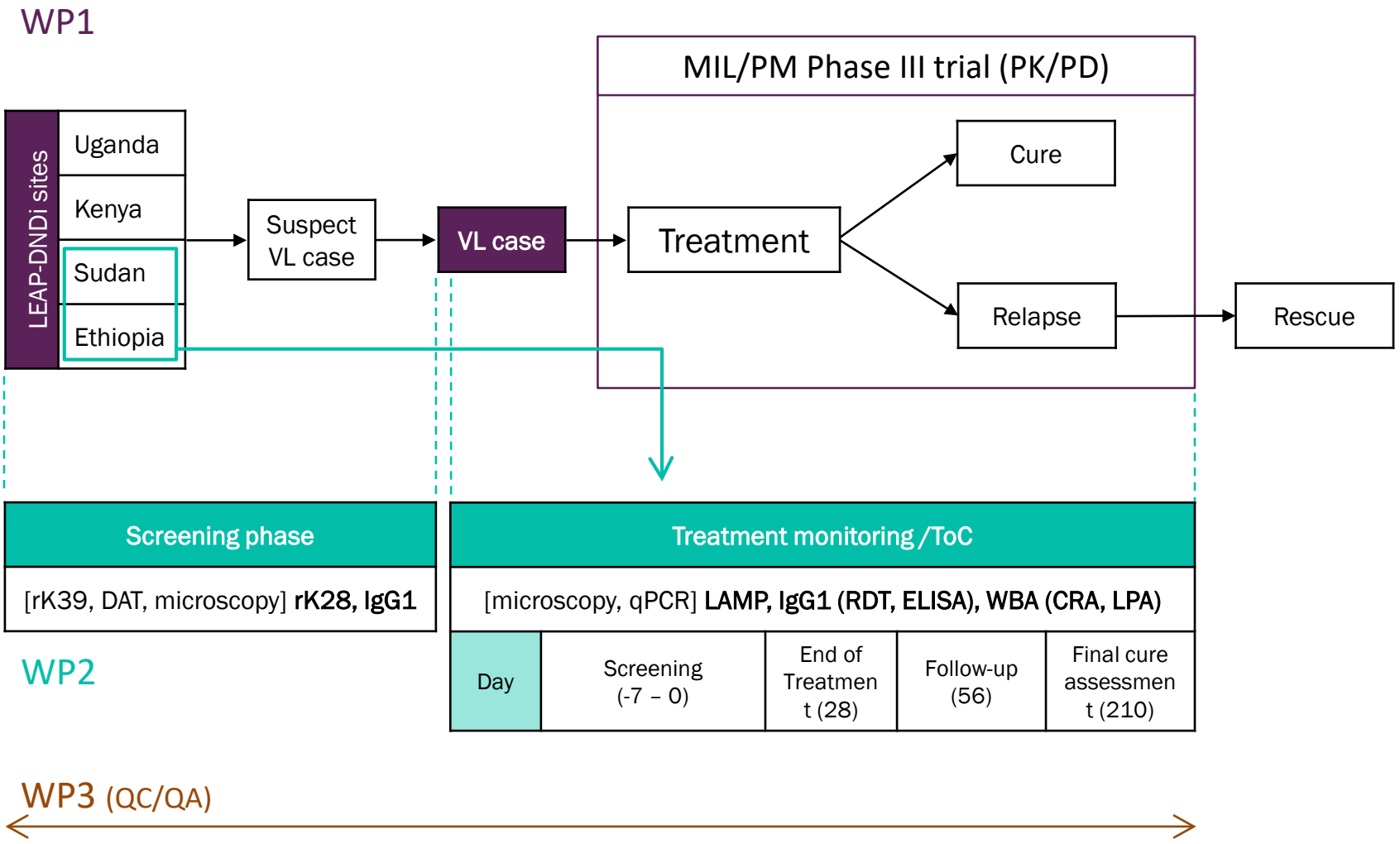
- Microscopy is used in the diagnosis of relapses, inclusion of patients in clinical trials and also as ToC
  - Variable sensitivity, invasive, risky
  - Difficult to harmonize pre- and post-treatment sample (can be a challenge in CT)

- In Africa (…), the efficacy of the best therapeutic option is ~ 90% (Alvest et al., CMR 2018)

ToC/TM study

DNA detectection	Humoral immune response	Cell-mediated immune response
LAMP	IgG1 RDT /ELISA	Lymphoproliferation assay (CPA), Cytokine release assay (CRA)
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



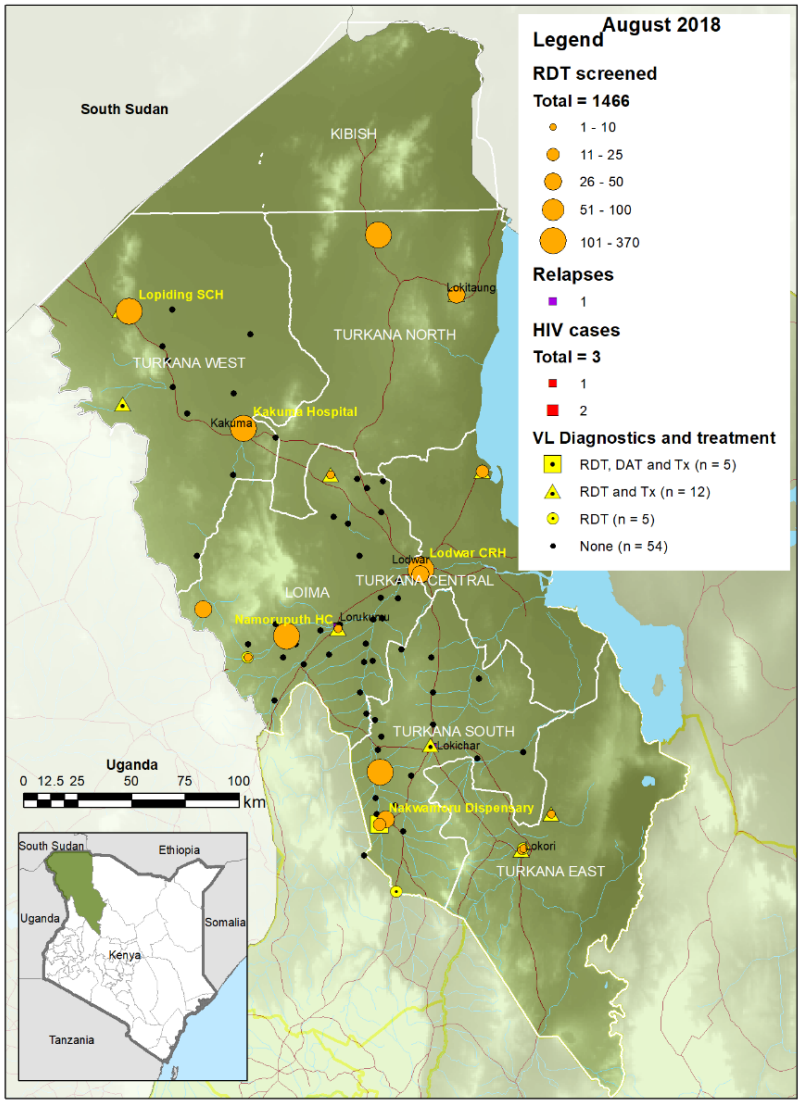
Accelerating Screening Study

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**

Health facilities offering VL diagnosis and treatment in Turkana county, Kenya



Thank you !

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EDCTP