"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

DNDi
Drugs for Neglected Diseases *initiative*

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).**

NEED	CURRENT METHODS	GAP	POTENTIAL SOLUTIONS
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

Diagnostics to sustain & monitor VL elimination – Pipeline

	Feasibility	Development	Evaluation	Demonstration (registered)	Scale-up
VL	• Leishmaniasis-RDT (Ag detection)		• Leishmania Antigen Detect ELISA (Inbios) • VL ELISA (Ag detection – Kalon)	• Loopamp Leishmania Detection Kit (NAAT) • STAT-NAT Leishmania (NAAT) • KAtex(Ag detection – Kalon)	
PKDL			• Loopamp Leishmania Detection Kit (NAAT; Eiken)*		
Treatment monitoring		• Leismaniasis IgG1-RDT (Ab-detection; Coris)	• Leishmania Antigen Detect ELISA (Inbios) • VL ELISA (Ag detection – Kalon)	• KAtex(Ag detection – Kalon)	

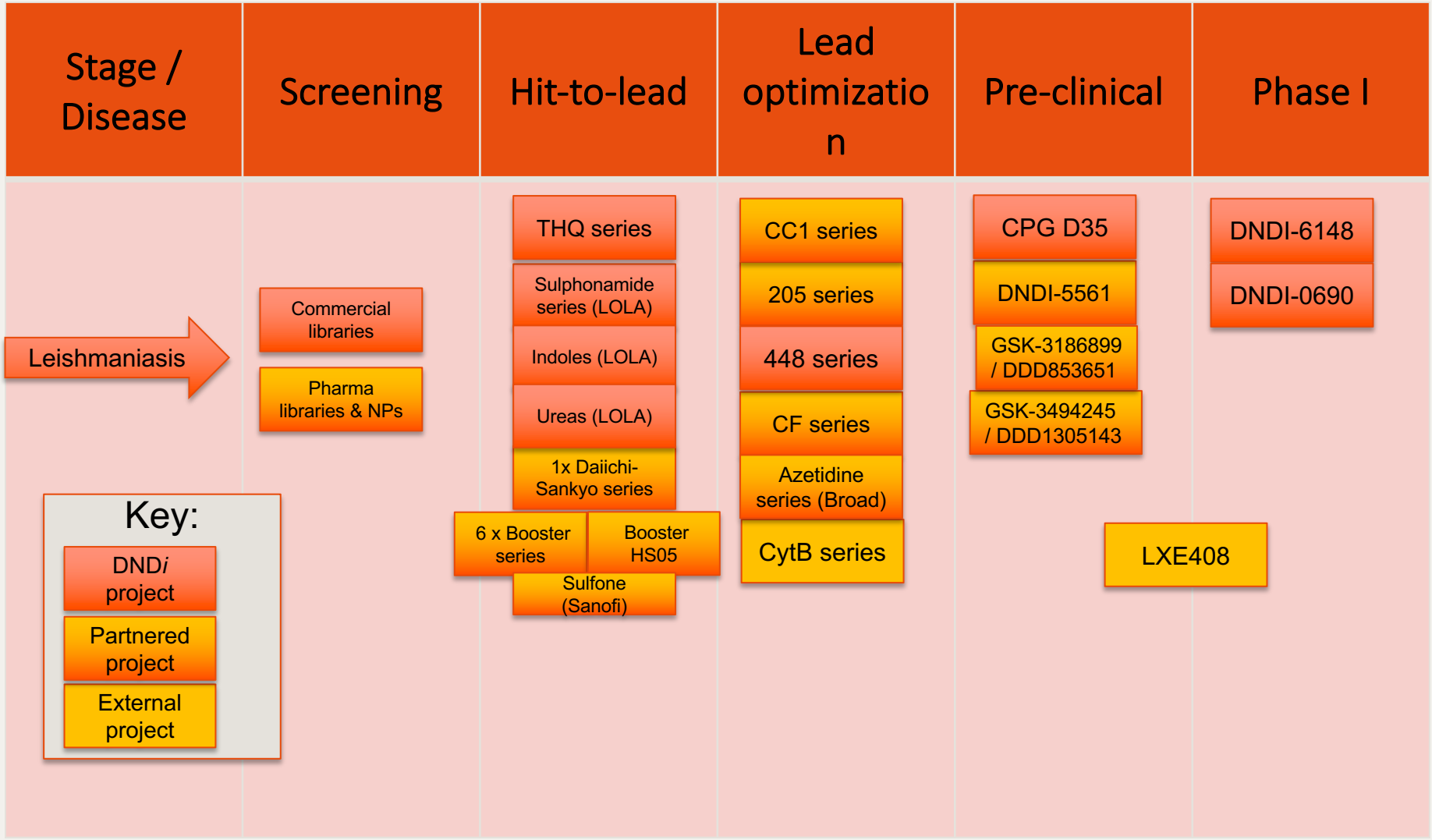
New treatment regimens in PKDL

- **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*)

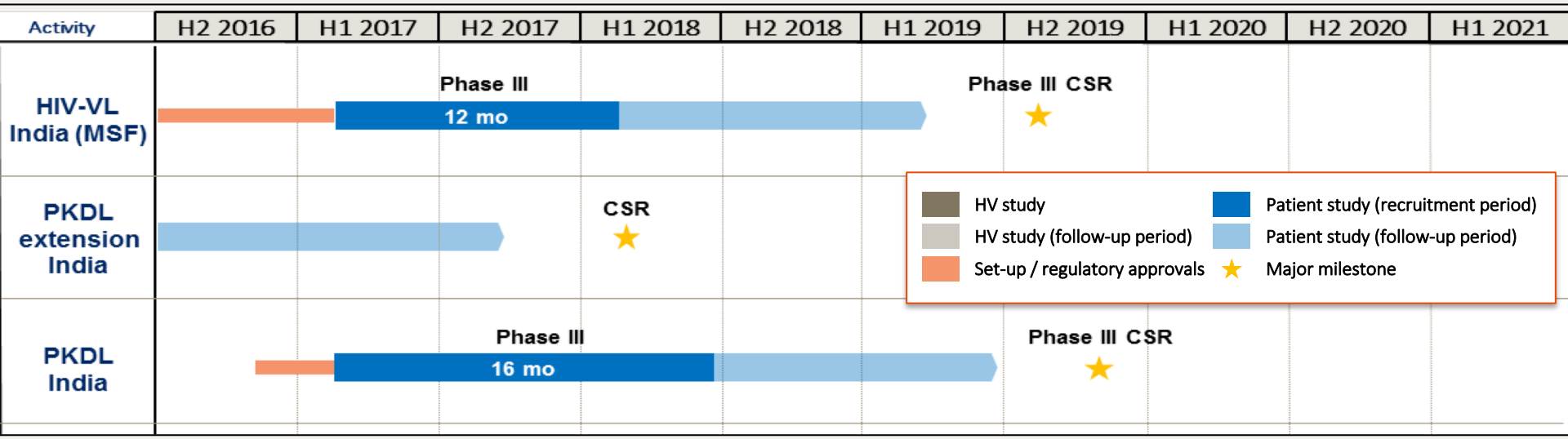
- **L-AMB 15 mg/kg, given over 15 days:** 273 patients assessed at 12 months (den Boer et al. 2018 CID)
  - All patients completed treatment without severe or serious adverse events
  - Complete or major improvement of lesions : 245 **(89.7%)** patients;
  - Completely cured: 213 (78.0%)
  - Lesions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

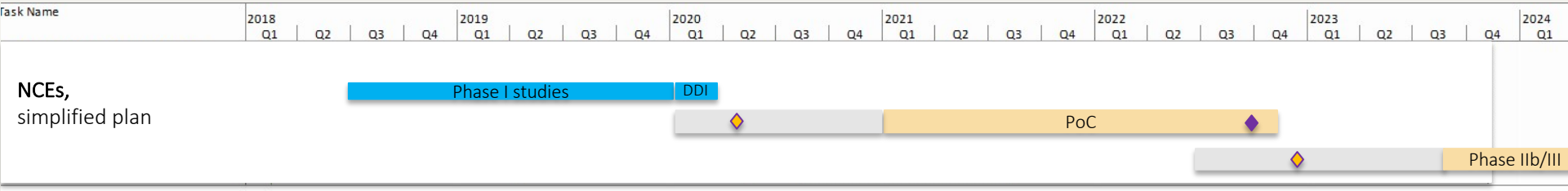
- **Ongoing CT (Started Q4 2017)**: To measure the safety and efficacy in the Indian Sub Continent:
  - L-AMB monotherapy regimen (total dose of 20 mg/kg)
  - L-AMB (total dose of 20 mg/kg) in combination with miltefosine daily for three weeks (allometric dosing)

Discovery/preclinical portfolio: March 2018

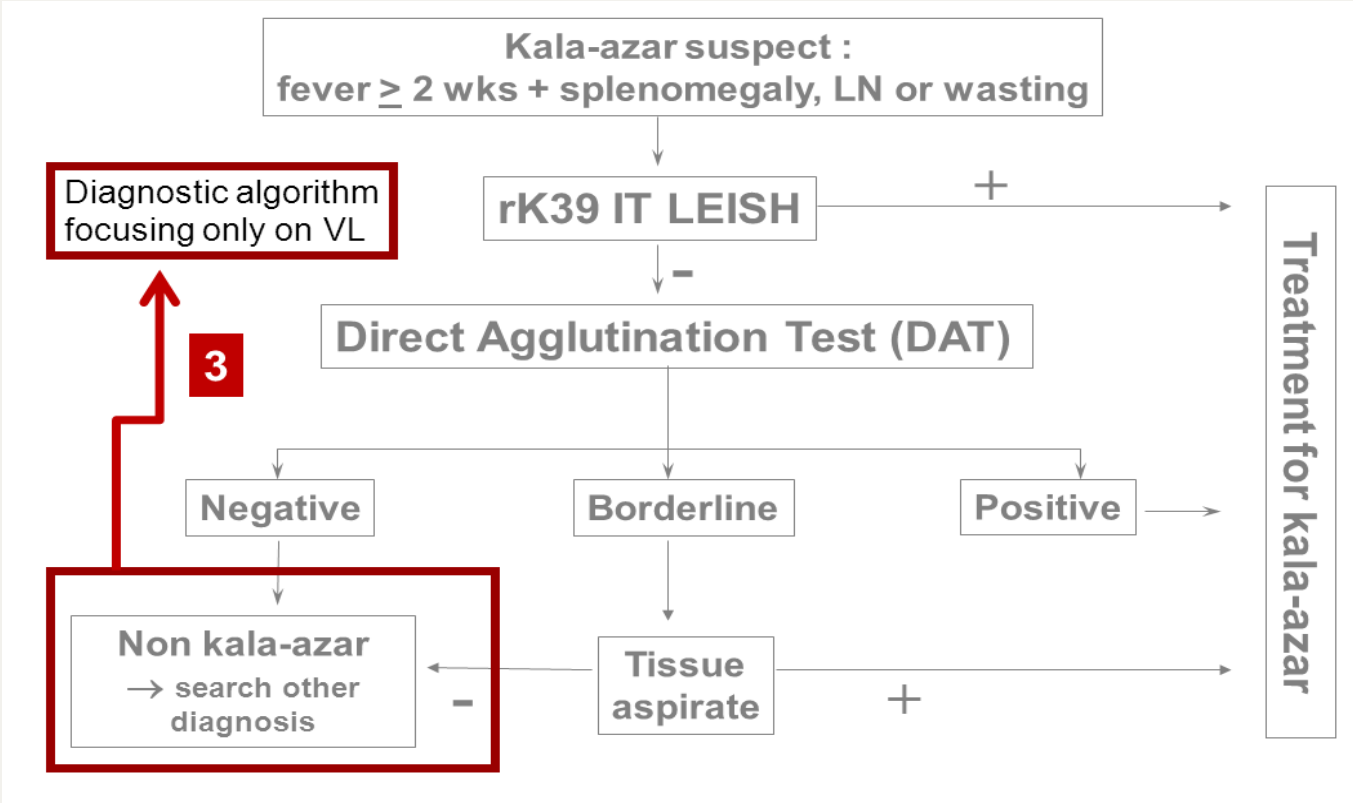


Project timelines





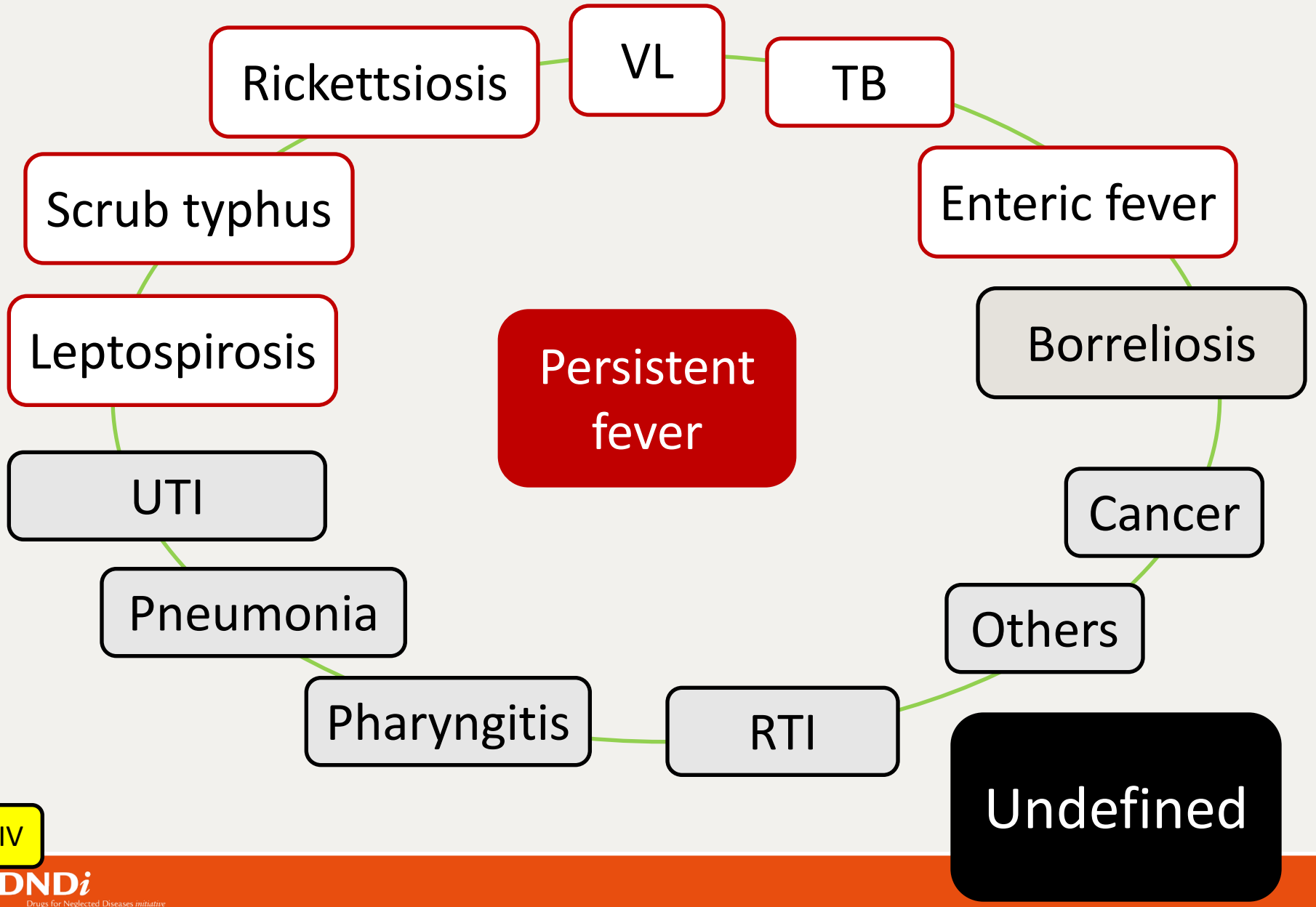
Limitations of VL diagnostic algorithms



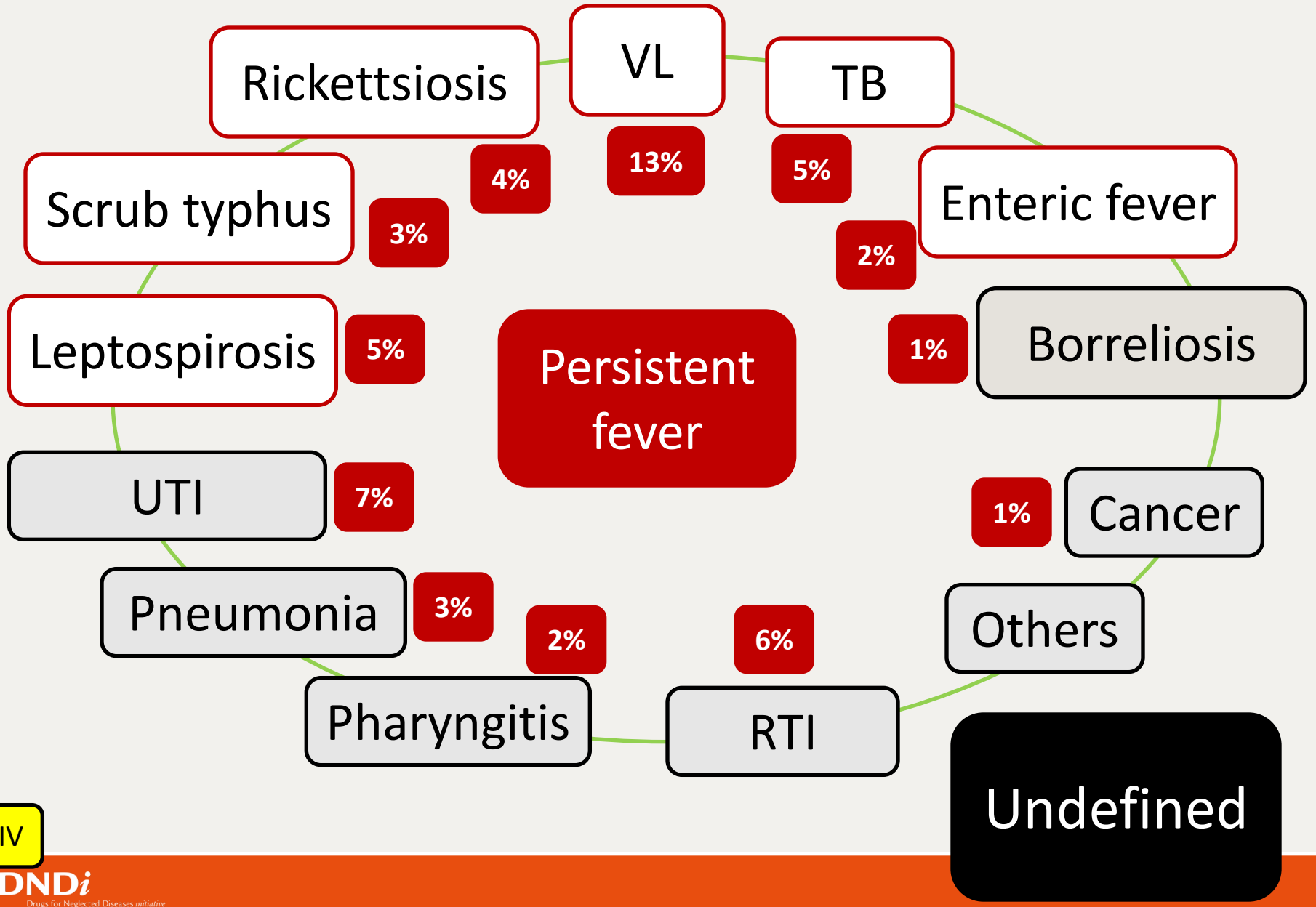
nidiag
Better Diagnosis of Neglected Infectious Diseases

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

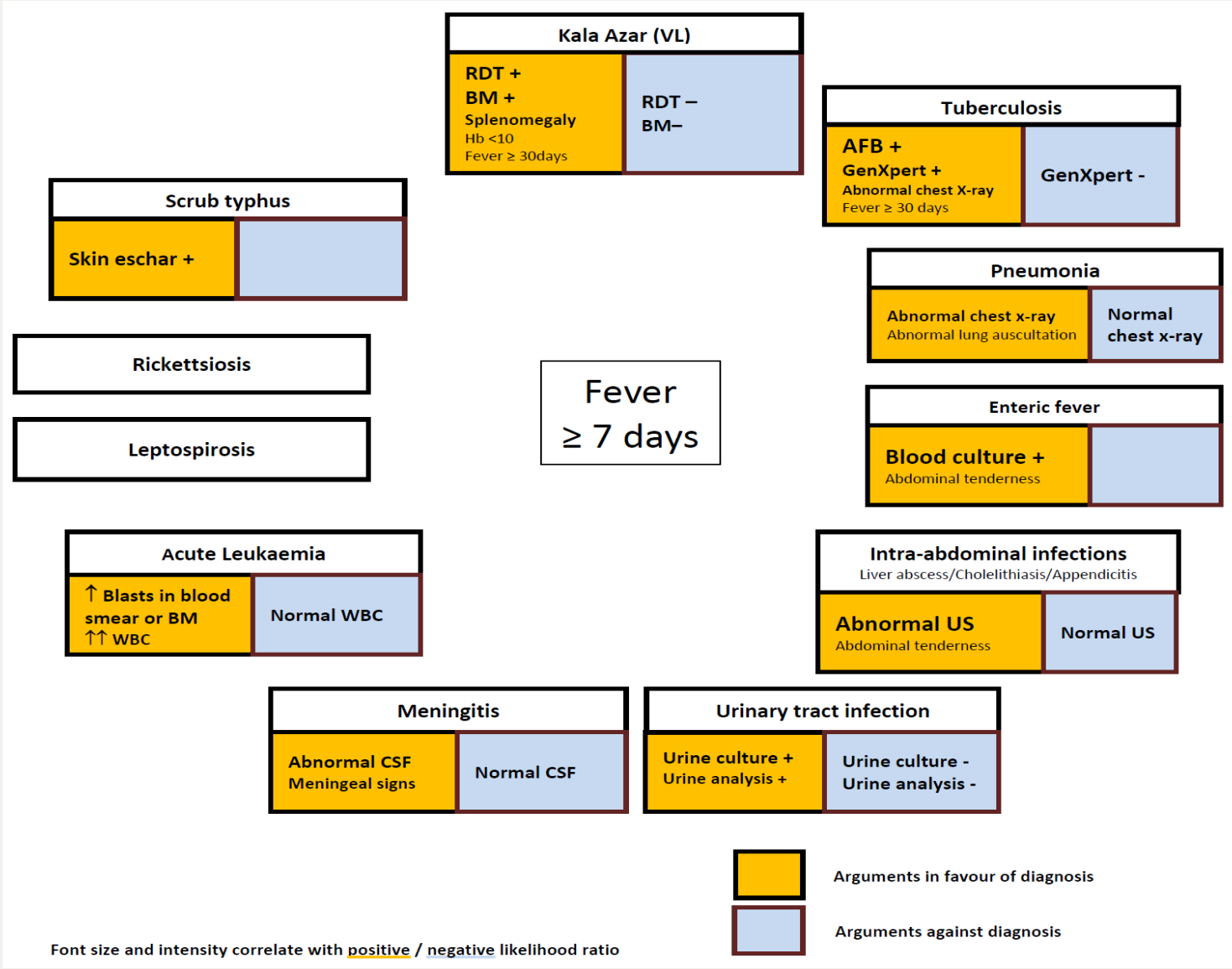
Diagnostic panorama (BPKIHS, Nepal)



Pre-test probabilities (BPKIHS)

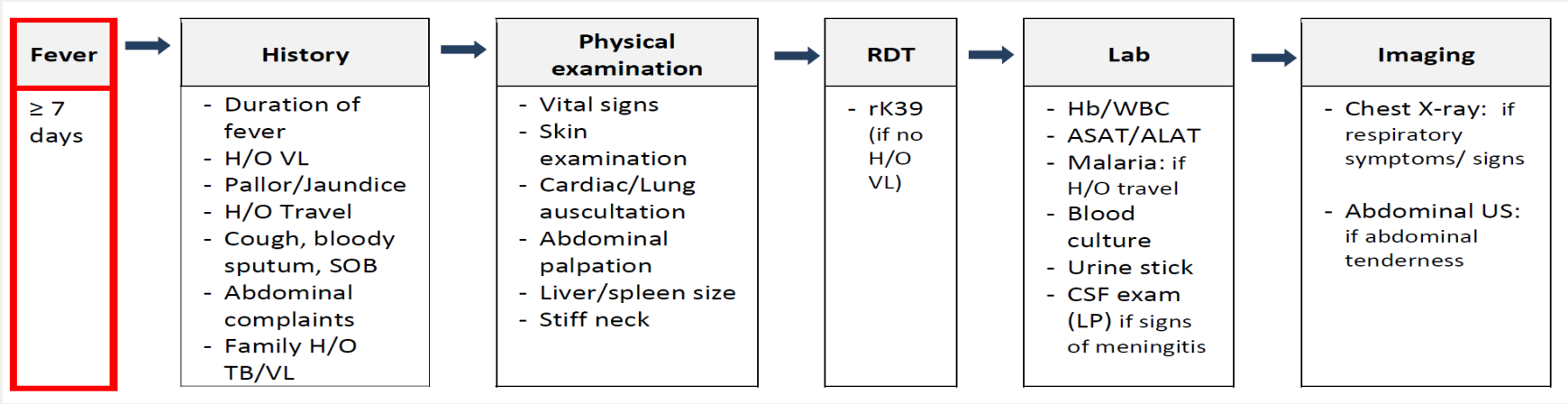


Diagnostic guidance (Nepal)



Diagnostic guidance – investigations

Nepal



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

DNDi
Drugs for Neglected Diseases *initiative*