Towards an arsenic-free oral treatment for human African trypanosomiasis due to *Trypanosoma brucei* rhodesiense: a new tool for disease elimination

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Conflict of Interest:
The author has declared no conflict of interest.

Introduction – Background and context on *Trypanosoma brucei* rhodesiense HAT

FACTS

Most acute and severe form of sleeping sickness transmitted by tse-tse flies

Targeted for elimination as a Public health problem by 2030 (WHO NTD roadmap)

CHALLENGES

Up to now, the only available treatment for advanced (stage 2) *T.b. rhodesiense* HAT was **melarsoprol,** an injectable **arsenic derivative** with high toxicity.

RESULTS

2018: Fexinidazole, a **simple all-oral, 10-day treatment for both stages** of the *Sleeping sickness due to T.b. gambiense is approved*.

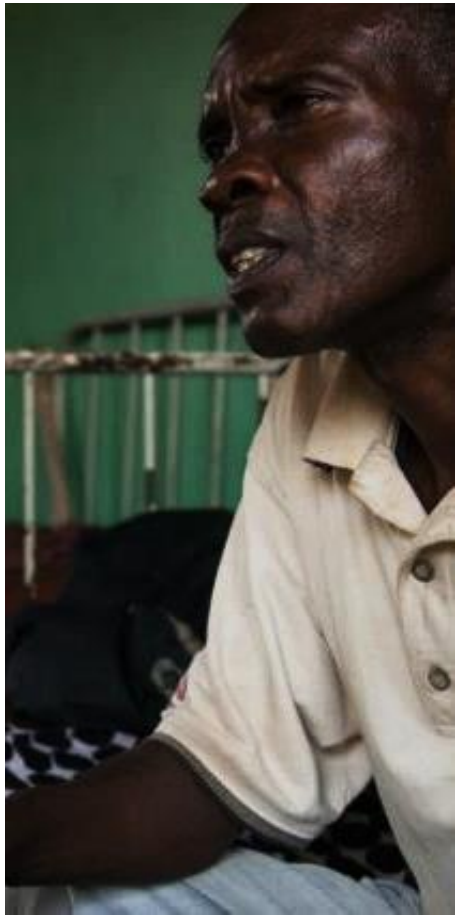
2019: Start of **Trial for *T.b. rhodesiense* HAT**

GOAL

2024: Extend fexinidazole indication to ***T.b. rhodesiense* HAT** (both stages).

Regulatory work under industrial partner responsibility

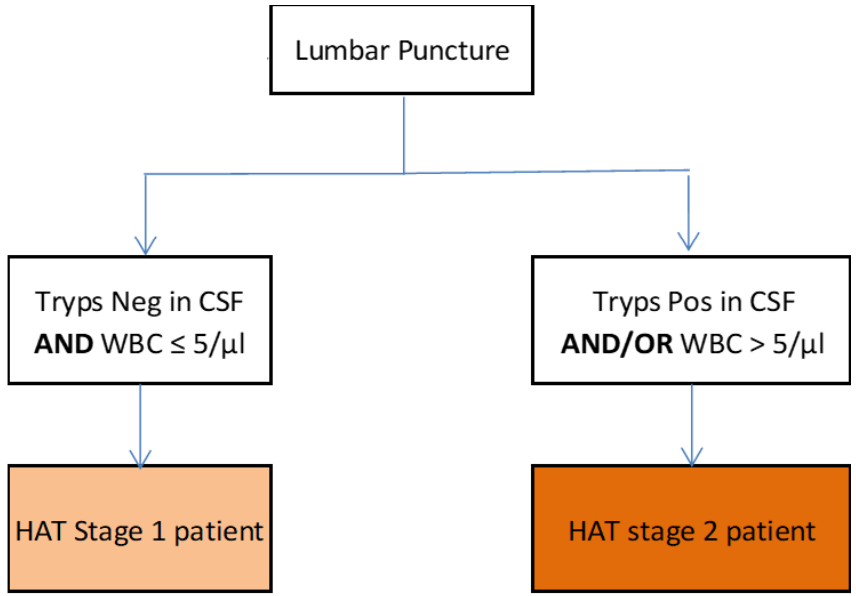
Preparing access to new treatments



source: DNDi

Introduction – Diagnosis of *Trypanosoma brucei* rhodesiense HAT

- Diagnosis is complex with 3 main steps:
  - Clinical signs and symptoms
  - Research for the parasites in body fluids (direct microscopy)
  - Staging disease progression, with analysis of cerebrospinal fluid after lumbar puncture
- Decision tree



WBC: white blood cells in CSF

source: DNDi

source: DNDi

Introduction - objectives of the study

- To show that fexinidazole offers an alternative to melarsoprol in stage-2 r-HAT patients and to suramin in stage-1 r-HAT patients
- **Primary objective**: to show that the fatality rate (r-HAT or treatment related deaths) at the end of hospitalization is < 8.5% in stage-2 patients (toxicity)
- **Main secondary objective**: to show that the proven failure rate (r-HAT or treatment-related death, or relapse) at or before 12 months in patients with stage 2 r-HAT treated was below the 12% unacceptable rate
- **Other secondary objectives**: efficacy on both stages, safety, *pharmakocinetics of fexinidazole*

Introduction – registration and funding and of the study

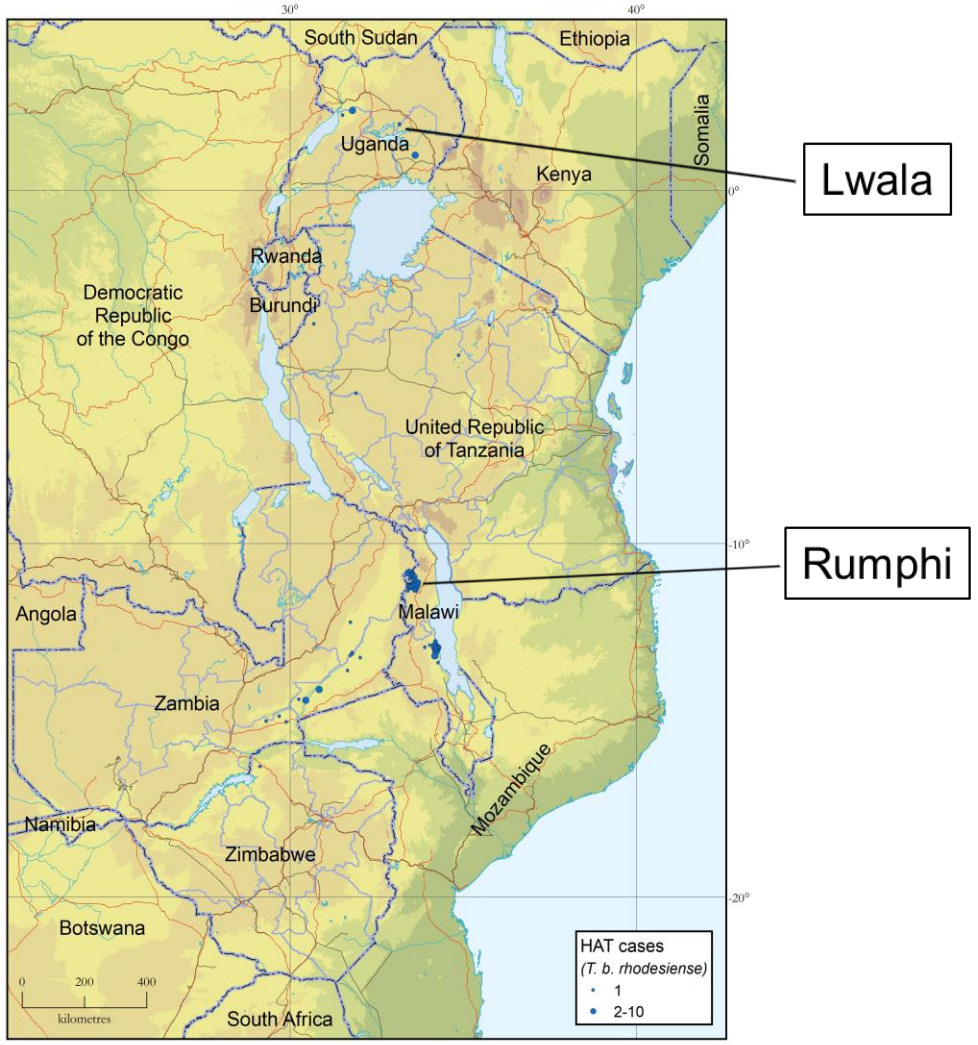
- Sponsored by DNDi
- co-funded by EDCTP and the Foundation for Science and Technology (FCT)
- Multi partners study with Epicentre responsible for data management and statistics
- Ethics:
  - National Health Science Research Committee in Malawi,
  - Independent Ethics Committee and the Vector Control Division–Research and Ethics Review Committee in Uganda
  - Commission Cantonale d'Ethique de la Recherche (Geneva, Switzerland).
- Registration ClinicalTrials.gov (NCT03974178)

Methods

- Design: Multicentre, open-label clinical trial, conducted in Uganda (Lwala hospital) and Malawi (Rumphi district hospital) (reference hospitals for HAT)
- Inclusion criteria: Patients with confirmed parasitological *T.b.* rhodesiense infection, ≥ 6 years old, ≥ 20 kg body weight and able to ingest at least one complete meal a day
- Schedule of events:

- Sample size calculation: need of 34 stage-2 evaluable patients at the end of hospitalisation, based on feasibility and a possible rejection that fatality rate is ≥ 8.5% (threshold agreed with WHO experts group)
- Statistics: Confidence intervals (CIs) estimated using Clopper-Person exact method; one-sided exact test at the significance level of 5%

Rhodesiense HAT cases in Estern and Southern Africa.
Period 2019–2020.



Source: WHO HAT Atlas

Results: patients disposition and baseline characteristics

- **Recruitment** 25 months + 12 months follow-up
  - First patient first visit: 29 Sept. 2019
  - Last patient last visit: 12 Oct. 2022
- Total of 45 patients included, 44 completed treatment

Baseline Characteristics	Total (N = 45)
Age in years – median	24
Male - n (%)	31 (68.9)
Female - n (%)	14 (31.1)
Pregnant women - n (%)	1 (2.2)
Stage	
- Stage 1 - n (%)	10 (22.2)
- Stage 2 - n (%)	35 (77.8)

- **Evaluable population**: 44 patients including 34 stage 2 and 10 stage 1
  - Non evaluable: 1 death unrelated to either treatment or r-HAT during treatment period in a stage 2 patient (Data safety monitoring board conclusion)

Results: primary & secondary efficacy endpoints

Primary objective: To show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalization in patients with stage 2 r-HAT was smaller than an unacceptable rate of 8.5%.

n (%), 90% CI	Stage 2 (N = 34)
Death possibly related to r-HAT or to fexinidazole	0 (0.0), [0.0 - 8.4] ; p=0.048

Main secondary objective: proven failure rate (r-HAT or treatment-related death, or relapse) at 12 months visits was below the 12% unacceptable rate

n (%), 90% CI	Stage 2 (N = 34)	Stage 1 (N = 10)	Total (N = 44)
Failure rate at M12	1 (2.9), [0.2 - 13.2] ; p=0.073	0 (0.0)	1 (2.3), [0.1 - 10.3] ; p=0.025

- 1 relapse at Week 9
- No failure in stage 1

Results: Safety

- Mainly digestive adverse events, small ECG QT prolongation (12 to 16 ms)
- 3 serious adverse events* (1 leading to death**)

System Organ class/ Preferred Term	Number of patients (%), related to fexinidazole
Hospitalization period	
Gastrointestinal disorders	10 (22.2%)
Vomiting	**6 (13.3%), 1**
Nausea	2 (4.4%), 0
Gastritis	**1 (2.2%), 1**
Investigations	9 (20.0%)
Electrocardiogram U-wave abnormality	**3 (6.7%), 1**
Electrocardiogram QT prolonged	**2 (4.4%), 2**
Electrocardiogram T wave abnormal or inverted	2 (4.4%), 0
Blood pressure increased	**1 (2.2%), 1**
Metabolism and nutrition disorders	4 (8.9), 0
Hypoalbuminemia	3 (6.7%), 0
Infections and infestations	3 (6.7%), 0
Malaria	2 (4.4%), 0
Blood and lymphatic system disorders	2 (4.4%), 0
Nervous system disorders	2 (4.4%), 0
Renal and urinary disorders	2 (4.4%), 0
**Acute kidney injury ** **	1 (2.2%), 0
Musculoskeletal and connective tissue disorders	1 (2.2%), 0
General disorders and administration site conditions	1 (2.2%), 0
Cardiac disorders	1 (2.2%), 0
Vascular disorders	1 (2.2%), 0

System Organ class/ Preferred Term	Number of patients (%), related to fexinidazole
Follow-up period	
Infections and infestations	2 (4.4%), 0
Pneumonia *	1 (2.2%), 0
Urinary tract infection *	1 (2.2%), 0

- pregnant woman: 3rd trimester. Healthy child after >1 year follow up

Conclusions

r-HAT trial results:

- Promising alternative to existing drugs
- Primary objective achieved, main secondary on both stages combined
- One relapse confirmed: same r-HAT strain
- Safety results are favourable (no new safety signals from what was known in *gambiense*-HAT)

Regulatory:

- EMA EU-M(edicines)4all procedure: positive scientific opinion received in December 2023
- WHO is preparing updated treatment guidelines
- Registration ongoing in the two countries (Uganda and DRC) to be followed by approval of use by the remaining endemic countries

HAT-r-ACC

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Best Science for the Most Neglected

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