Actualités de la Trypanosomiase Humaine Africaine

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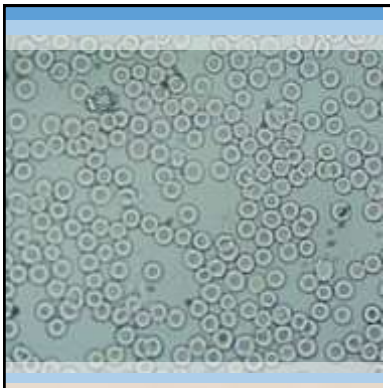

Human African Trypanosomiasis Sleeping sickness (HAT)

- Neglected tropical infection
  - Occurring exclusively in sub-saharan Africa
  - Fatal
- Trypanosomes: Extra-cellular parasites (15-30 µm)
- Transmitted by tsetse fly (*Glossina*)
  - Other transmission: Congenital (transfusion, accident)

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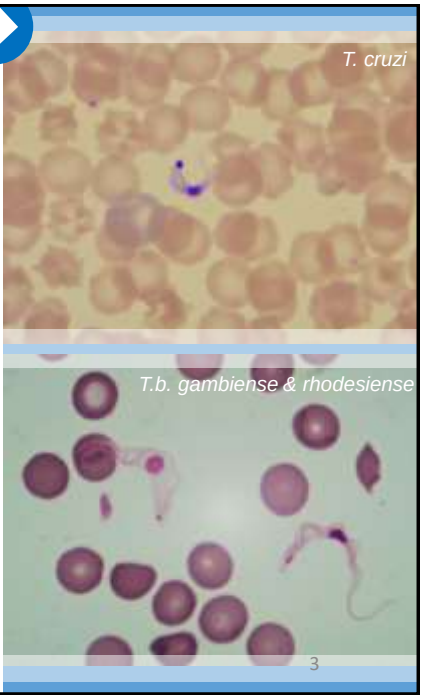
Classification

Genus	Section	Subgenus	Species	Subspecies
Trypanosoma	Stercoraria	Megatrypanum	*T. theileri, T. melophagium*	
		Herpetosoma	*T. lewisi, T. musculi, T. microti*	
		Schizotrypanum	*T. dionisii,* ***T. cruzi***	
	Salivaria	Tejeraia	*T. rangeli*	
		Duttonella	*T. uniforme, T. vivax*	
		Nanomonas	*T. simiae, T. congolense*	
		Pycnomonas	*T. suis*	
		Trypanozoon	*T. evansi, T. equiperdum,* ***T. brucei***	*T.b. gambiense* *T.b. rhodesiense* *T.b. brucei*



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2 subspecies, 2 disease forms

Trypanosoma brucei gambiense

- 95% of cases
- West and Central Africa
- Anthroponosis
- Low parasite numbers in blood
- Chronic, fatal after several years

Trypanosoma brucei rhodesiense

- 5% of cases
- East and Southern Africa
- Zoonosis
- High parasite numbers in blood
- Acute, fatal after weeks / months

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T.b. gambiense

- Anthroponosis:
  - Risk defined by
    - Contact with *G. palpalis*
    - Rainforest, wooded areas along rivers, mangrove
  - Risks:
    - Villages at rivers/lakes/mangroves
    - River crossing, water collection, washing sites, fish farming
    - Humid forest areas: coffee or cacao plantations
    - Sometimes close to large cities
  - Animal reservoir:
    - Domestic (pig) & wild
    - Role in transmission not well known

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T.b. rhodesiense

- Zoonosis
  - Animal reservoir
    - Wild: antelopes, zebra, hyena, lion, warthog, ...
    - Domestic: Cattle (cfr Uganda)
  - Risk defined by
    - Wild animals/cattle & tsetse
  - People at risk:
    - Honey gatherers, firewood collectors, fisherman
    - Game wardens & poachers
    - Farmers
    - Tourists

« We were warned that Tarangire park had a problem with tsetse flies, so Ruth Ann is ready with the swatter! »

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Disease presentation

- 1st hemo-lymphatic stage
  - Dissemination & proliferation
  - Trypanosomes in blood and lymph
- 2nd meningo-encephalitic stage
  - Central nervous system invasion
    - *T.b. gambiense* 16 months
    - *T.b. rhodesiense* 3-5 months
  - Evolution to coma and death

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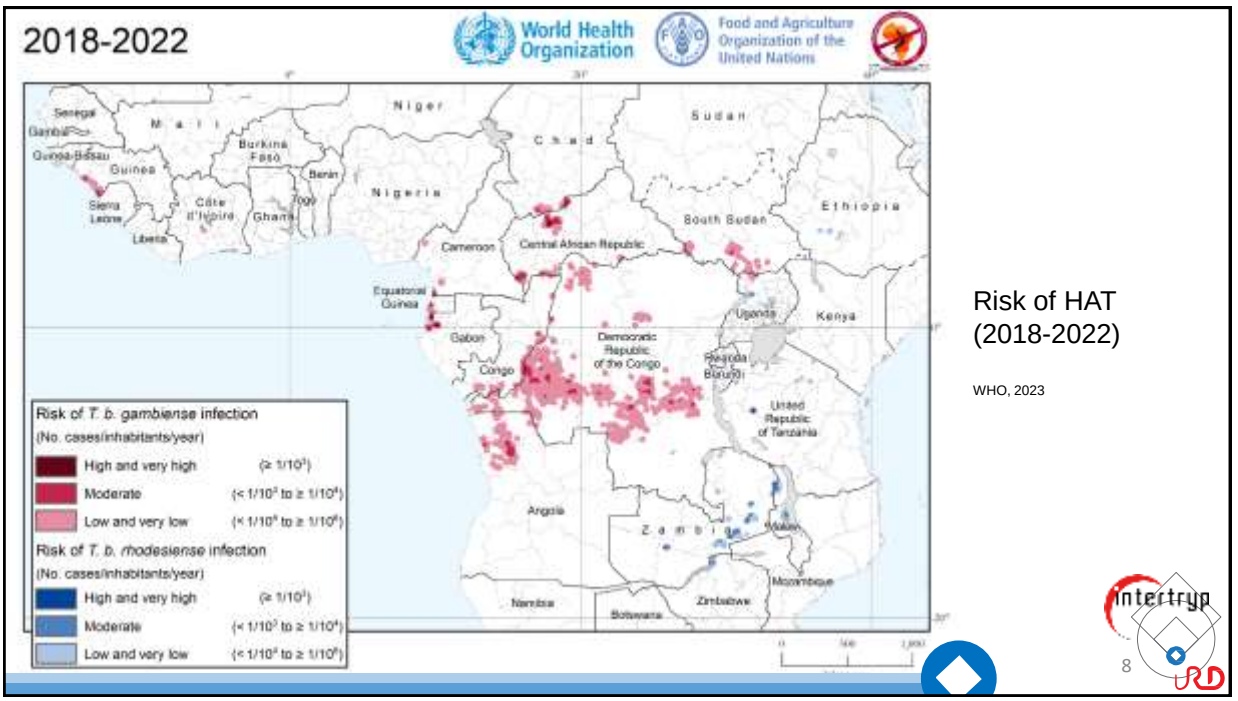

Risk of HAT (2018-2022)

WHO, 2023

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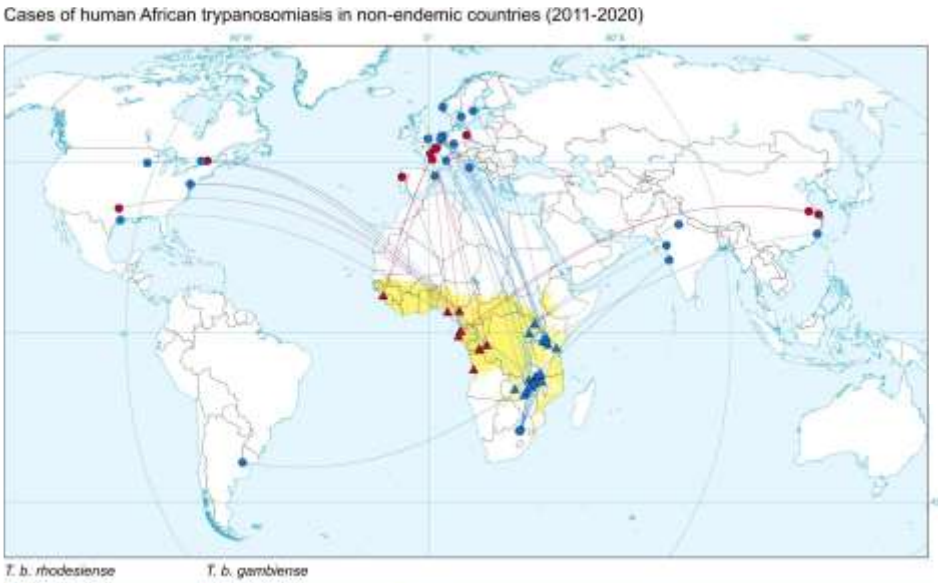
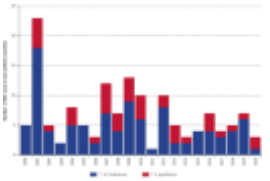


2011-2020:

49 export HAT cases (Franco et al., 2022)



- 49% Europe (24/49)
  - France: 7/49, zero since 2020
- 22% SA

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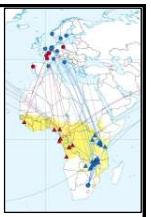
Characteristics export HAT cases



T.b. gambiense

- 29%
- Origin: DRC, Gabon, Guinea, Cameroon, Angola, Nigeria
- Risk factors: Immigrants from endemic countries (71%), long professional activity in endemic areas (28%), congenital
- Diagnosis: Parasitology (64%)
  Serology & PCR (support ITM-Antwerp)
  After 1-2 years, or later
- Disease stage: 93%, 2nd neurological stage
- France: 6/7 HAT cases *T.b. gambiense*

T.b. rhodesiense

- 71%
- Origin: Zambia, Tanzania, Uganda, Malawi, Kenya, Zimbabwe
- Risk factors: Exposure to wildlife reservoir in protected areas [Tourists (63%), hunters (17%), professional activity (20%)]
- Diagnosis: Parasitology (91% blood smear)
  After 1-2 weeks, 1 month at last
- Disease stage: 91% 1st stage
- France: 1/7 HAT cases *T.b. rhodesiense*

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HAT cases in France (2011-2020)

Time	Place diagnosis	Place infection	Sex/age	Activity	Diagnosis	Stage	Chancre	Treatment
12/2012	Chamberry	Zambia	M37	Pilot (tourism)	Blood smear	1	no	suramin
01/2013	Paris	Gabon	M29	Trader	PCR, IFAT, CATT	2	yes	NECT
06/2013	Tours	RDC	F22	Immigrant	CSF	2	No	Eflornithine
06/2013	Tours	RDC	M1	Immigrant	CSF	2	No	Eflornithine
08/2016	Limoges	RDC	F21	Immigrant	CSF	2	No	NECT
12/2016	Meaux	Guinea	M55	Immigrant	PCR	2	No	NECT
05/2018	Creteil	Guinea	F45	Immigrant	Blood smear	2	no	NECT

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Symptoms & signs

1st stage, hemo-lymphatic

- Headache, irregular fever
- Lymphadenopathy (*T.b. gambiense*)
- Chancre (non-endemic cases *T.b. rhodesiense*)
- Weakness & weight loss
- Pruritus
- *T.b. rhodesiense:* Electrocardiogram changes, multi-organ involvement, myocarditis

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Symptoms & signs

2nd stage, meningo-encephalitic

- Psychiatric disturbances (→ taken for insanity)
  - Change in behaviour
  - Indifference / agitation
  - Aggresivity, depression, hallucinations, delirium
  - Dementia
- Motor function abnormalities
  - Muscle tone disorders
  - Abnormal movements, abnormal walking, paralysis
  - Abnormal primitive reflexes
- Sensory disorders
  - Hypersensitivity
  - Hyperesthesia with delayed pain out of proportion

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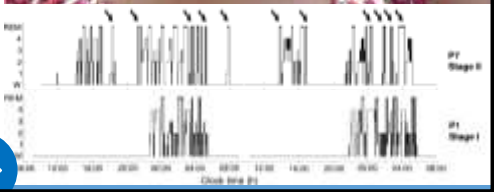
Symptoms & signs

2nd stage, meningo-encephalitic

- Sleep disturbances
  - Disruption of sleep-wake cycle
    - Daytime somnolence, nocturnal insomnia
    - Uncontrollable sleep
  - Alterations in sleep structure (polysomnography)
    - Sleep onset REM (SOREM) sleep episodes:
      REM preceded by wakefullness
      in stead of REM preceded by non-REM



Buguet et al 2005
doi.org/10.1016/j.actatropica.2004.10.001

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Differential diagnosis

- 1st stage:
  - Malaria
  - HIV, enteric fever, viral hepatitis, tuberculosis, viral hemorrhagic fever
- 2nd stage:
  - Bacterial meningitis, cerebral tuberculosis, HIV infection, cryptococcal meningitis, cerebral toxoplasmosis, CNS lymphoma , neurosyphilis, typhoid encephalopathy, psychiatric illness
- Misdiagnosis: frequent

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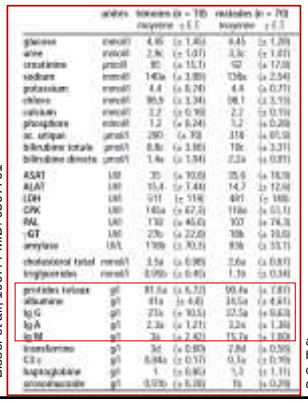
HAT laboratory blood findings

T.b. gambiense

- Elevated IgM & IgG (auto- & cross reacting Abs)
- Decreased albumine



Bisser et al., 1997. PMID: 9507761

a $p<0.0001$
b $p<0.001$
c $p<0.01$
d $p<0.05$

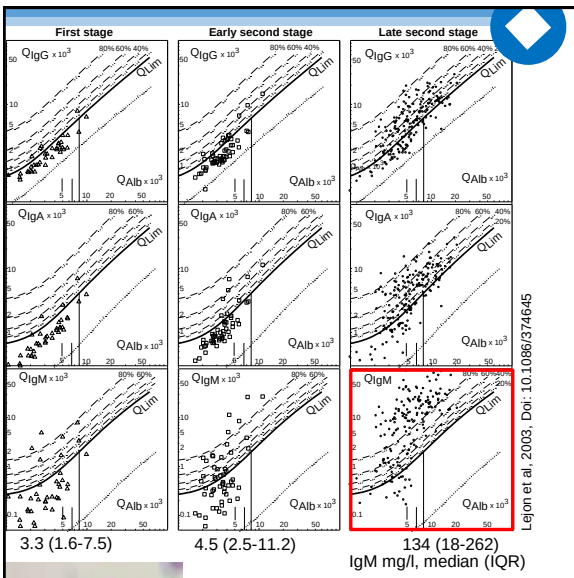
T.b. rhodesiense

- Thrombocytopenia, anemia, leukocytosis
- Abnormalities of renal and hepatic function

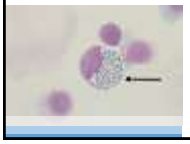
Laboratory findings on presentation in selected patients with severe East African trypanosomiasis, South Africa, 2004–2018.

Laboratory investigation	Average value (range)	Reference value or range
Haemoglobin	12.8 (10.9–15.1) g/dl	14.5–18.5 g/dl
Leukocyte count	6.0 (0.77–16.93) × 10^9/l	3.9–9.9 × 10^9/l
Platelet count	27.2 (5–79) × 10^9/l	150–450 × 10^9/l
Aspartate aminotransferase (AST)	340 (132–696) U/l	<38 U/l
Alanine aminotransferase (ALT)	351 (93–943) U/l	<50 U/l
Gamma glutamyltransferase (γGT)	330 (43–499) U/l	<60 U/l
Alkaline phosphatase (ALP)	304 (101–407) U/l	40–130 U/l
Bilirubin (total)	233 (72–511) µmol/l	5–21 µmol/l
Bilirubin (conjugated)	147 (37–248) µmol/l	0–5 µmol/l
Urea	17.1 (3.4–49.3) mmol/l	<8.6 mmol/l
Creatinine	241 (51–790) µmol/l	64–104 µmol/l
C-reactive protein (CRP)	187 (121–376) mg/l	<5 mg/l
Procalcitonin	2.9 (0.41–5.53) ng/ml	0–0.05 ng/ml

Frean et al., 2018, doi: 10.1016/j.ijid.2018.08.012



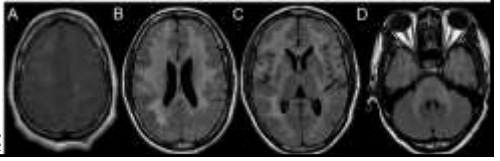
Lejon et al. 2003, Doi: 10.1086/374645



Lestrade-Carluer De Kyvon et al, 2016

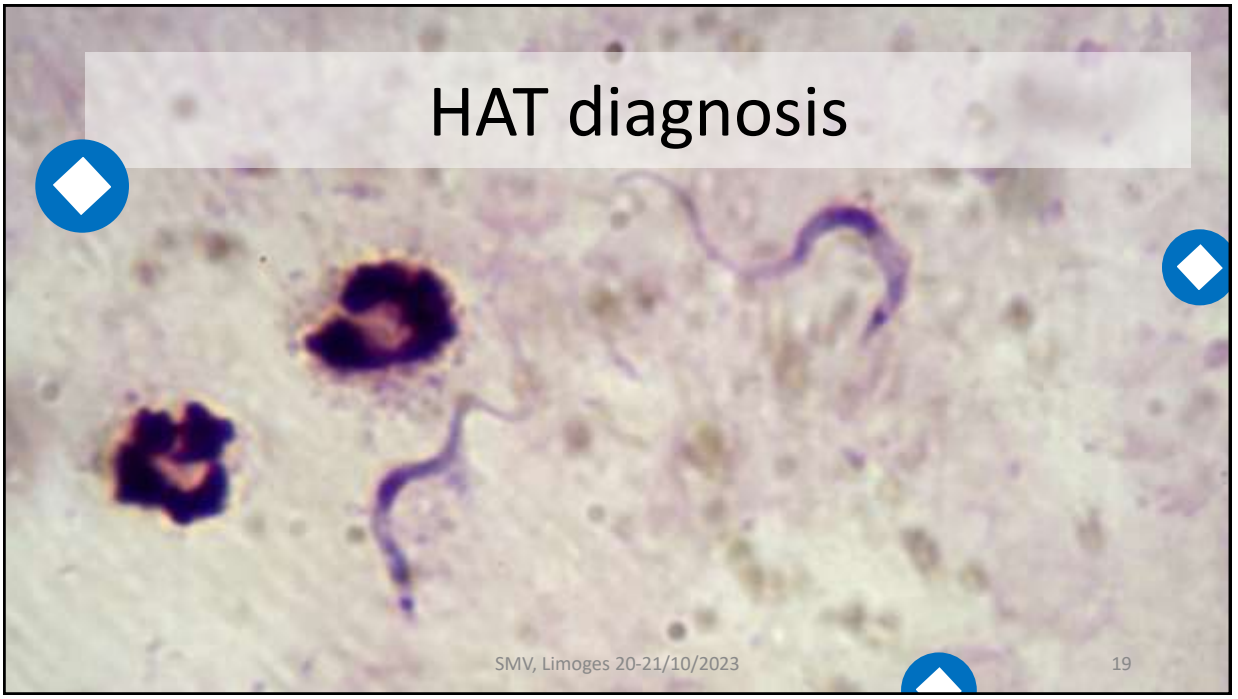
CSF abnormalities

- Intrathecal IgM response, moderate blood-CSF barrier dysfunction
- Increased cytorachia (B-lymphocytes)
  - Mott's cells (IgM-filled morular cells)
- Brain MRI: not useful:
  - supratentorial and infratentorial T2 hyperintensities affecting white matter and basal ganglia
  - perivascular and leptomeningeal enhancement



Gaillot et al 2017, doi.org/10.1371/journal.pntd.0005642

HAT diagnosis



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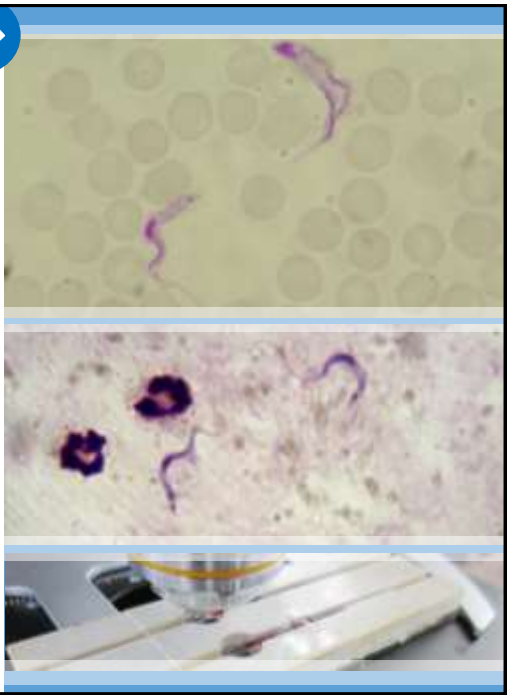
Parasitology

- Lymph node/chancre aspirate (40-60% sens)
- Blood
  - Stained:
    - Thick blood film (40% sens)
      do not confuse with platelets!!!
    - Thin blood film (*T.b. rhodesiense*)
  - Fresh blood examination (10% sens)
  - Micro-hematocrite centrifugation (60% sens)
    - Trypanosomes concentrate in buffy coat
    - Difficult recognition (phase contrast + movement)
  - Mini-anion exchange centrifugation technique (85% sens): availability!
- Cerebrospinal fluid
  - During WBC count or after centrifugation



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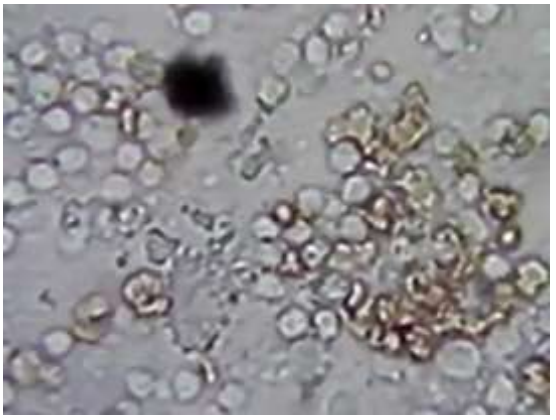

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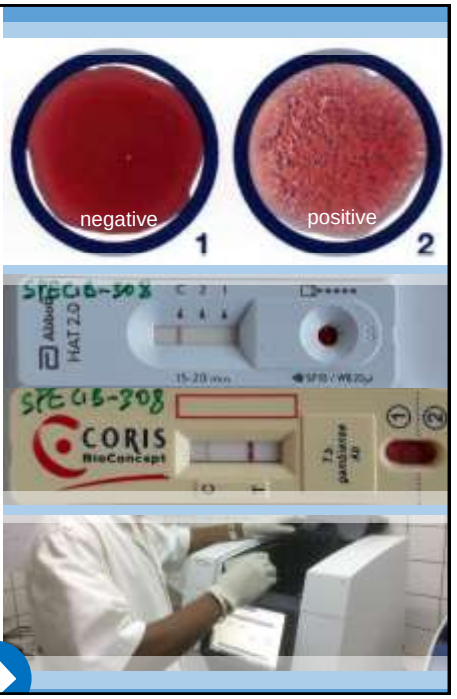
Diagnosis of HAT- Other

- Antibody detection
  - *T.b. gambiense* + *rhodesiense*: IFAT, ELISA
  - *T.b.* gambiense: CATT, RDTs (Coris, Abbott)
- Molecular tests
  - *T.b. gambiense* + *rhodesiense:* Target *Trypanozoon*
    - PCR: 18S rRNA gene (Deborggraeve et al. 2011)
    - RT-qPCR: Spliced Leader RNA (Ilboudo et al., 2015)
    - *Trypanozoon* RT-qPCR multiplex: 18S rRNA + TBR-177T DNA + RNAse P (Van Reet, ITM Antwerp)
    - SHERLOCK4HAT (Sima et al., 2022)
  - *T.b. rhodesiense:* Target SRA (Radwanska et al., 2002)



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Treatment of HAT

- Drugs available via WHO - directly or from institutions keeping stocks (University hospital Antwerp, Hospital clinic Barcelona, Swiss Tropical and Public Health Institute, …)

	T.b. gambiense	*T.b. rhodesiense*
Hemo-lymphatic, 1st stage: - WBC ≤ 5/µl, AND - No trypanosomes in CSF	**Pentamidine**	**Suramin** (Pentamidine)
Meningo-encephalitic, 2nd stage: - WBC < 5/µl, OR - Trypanosomes in CSF	**Melarsoprol**	
	Eflornithine + **NECT**	

Fexinidazole | Acoziborole

° 202X?

° 2001 | ° 2009 (EML) | ° 2019 | ° 2024?

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Treatment: 1st stage

T.b. gambiense

- Pentamidine
  - 7 daily IM injections 4 mg/kg/day
  - Adverse reactions:
    - Generally well tolerated
    - Mild nephrotoxicity, hypoglycemia

T.b. rhodesiense

- Suramin
  - Test dose of 4-5 mg/kg on day 1,
    5 IV injections of 20 mg/kg every 3-7 days
  - Adverse reactions:
    - Hypersensitivity
    - Proteinuria, stomal ulceration

Intertryp

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Treatment: 2nd stage

T.b. gambiense

- Nifurtimox-Eflornithine
  Combination Therapy (NECT)
  - Nifurtimox oral 15 mg/kg/day, 10 days
    Eflornithine infusion 400 mg/kg/day
    (every 12 hours), 7 days
  - Adverse reactions: Vomiting, dizziness, headache, …
- Eflornithine
  - Infusion 400 mg/kg/day (every 6 hours), 14 days
  - Adverse reactions: fever, pruritus, hypertension, vomiting, diarrhea, abdominal pain, headache, neutropenia

T.b. rhodesiense

- Melarsoprol
  - 2.16 mg/kg/day for 10 days
  - Adverse reactions: severe
    Acute reactive encephalopathy:
    up to 10% mortality → "killer drug"
- Fexinidazole (from 2024?)
  - >6 Yrs, >20 kg (1st & 2nd stage)
  - Day 1-4: 1800mg once daily, day 5-10: 1200mg once daily
  - Adverse reactions: Digestive problems, insomnia, headache

Intertryp

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Resources

Literature

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- Frean et al., 2018. Clinical management of East African trypanosomiasis in South Africa: Lessons learned. Int J Infect Dis. 75:101-108. doi: 10.1016/j.ijid.2018.08.012
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- WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva: World Health Organization; 2019. https://www.who.int/publications-detail-redirect/9789241550567
- BMJ Best Practice https://bestpractice.bmj.com/topics/en-us/9999
- UpToDate https://www.uptodate.com/contents/human-african-trypanosomiasis-epidemiology-clinical-manifestations-and-diagnosis ; https://www.uptodate.com/contents/human-african-trypanosomiasis-treatment-and-prevention

Diagnosis & treatment

- Diagnosis: ITM Antwerp
  - https://labo.itg.be/fr/
  - ✉ krl-admin@itg.be
    ☎ +32 (0)32476409
- Drugs: WHO NTD department
  - Francoj@who.int
  - Priottog@who.int

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