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Trypanosomiase humaine africaine: progrès et stagnation

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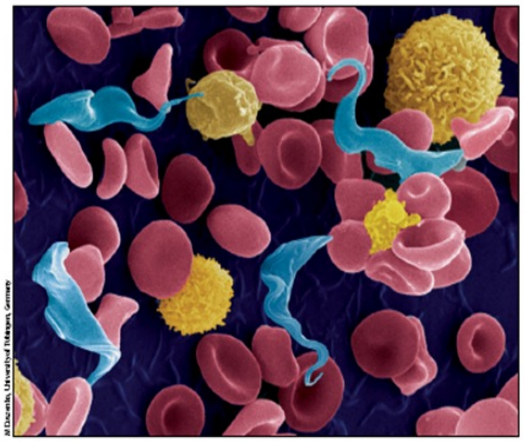
Déclaration d'intérêts de 2014 à 2022

- **Intérêts financiers : NON**
- **Liens durables ou permanents : NON**
- **Interventions ponctuelles : NON**
- **Intérêts indirects : NON**

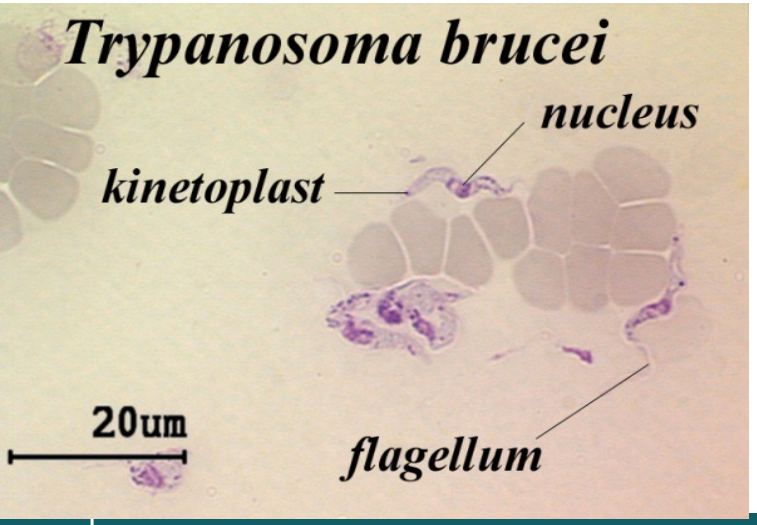
Outline human African trypanosomiasis (HAT)

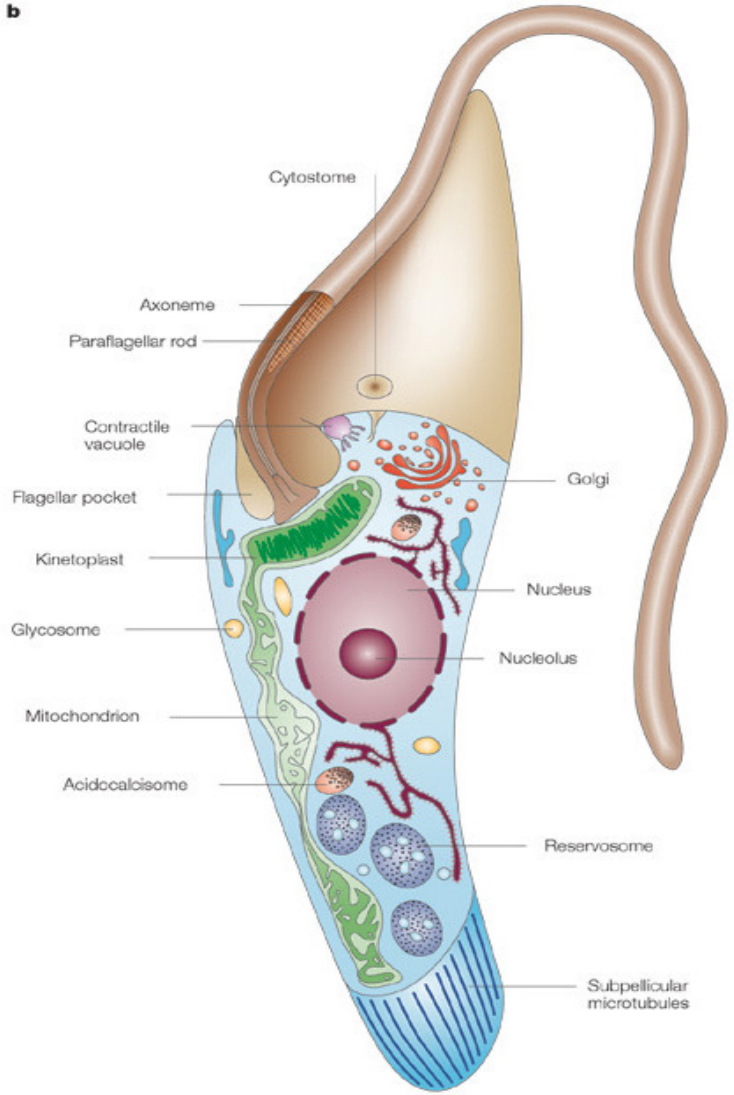
- Parasite and vector
- Current epidemiology
- Clinical presentations
- Diagnosis of HAT
- Treatment of HAT
- Control activities (West African HAT)



Parasite: *Trypanosoma brucei*

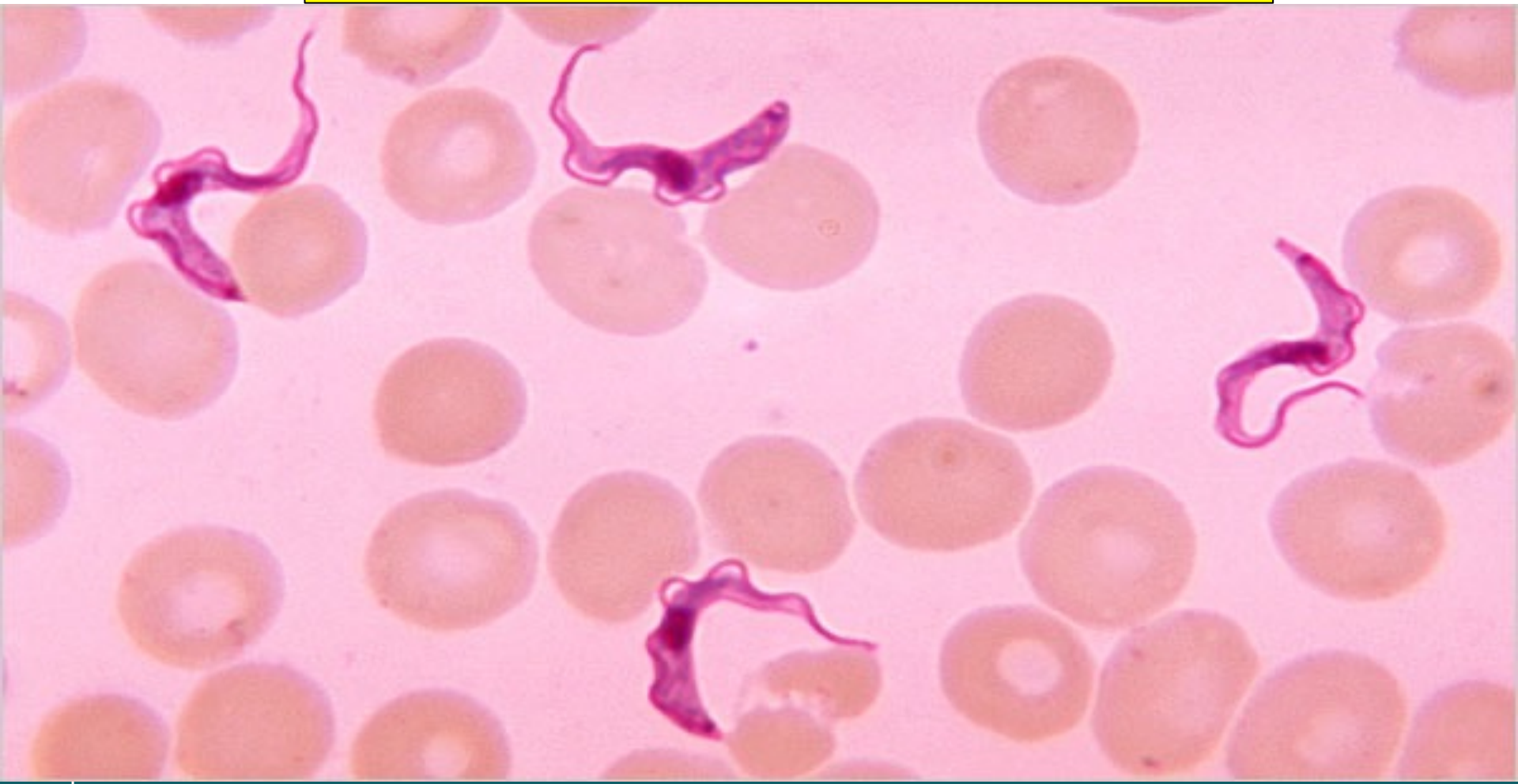
- Eukaryote
- Nucleus
- Kinetoplast (big mitochondrium)
- Flagellum
- Wavy membrane



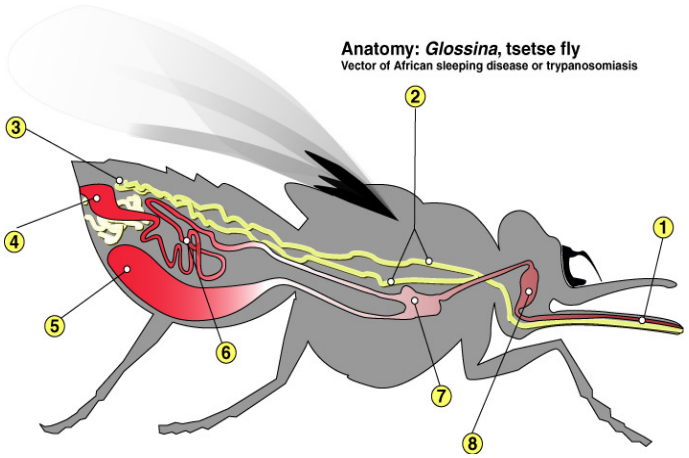


Parasite: *T. brucei gambiense & T. brucei rhodesiense*

Morphologically indistinguishable



Vector: *Glossina*, life cycle



Tsetse flies suck (infected) blood every 3-4 days

99% of parasites dies in insect stomach

Some transform in procyclic (midgut) and then

metacyclic trypomastigotes (salivary gland)

Tsetse become infectious 2-3 weeks after bloodmeal

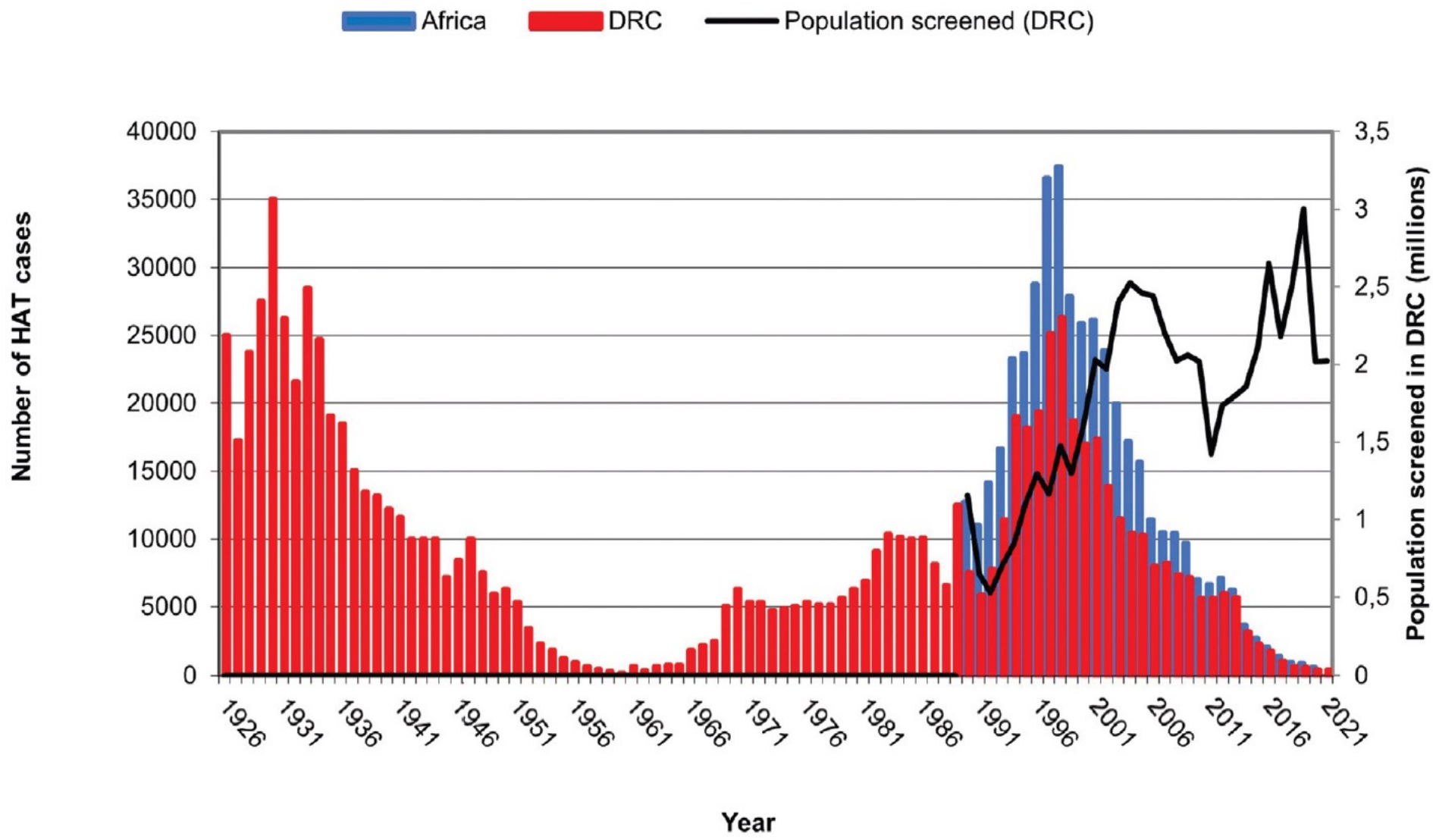
Tsetse flies live a few months

T. b. gambiense is an (epidemic) anthroponosis in Central and West Africa

T. b. rhodesiense is a sporadic zoonosis in East Africa

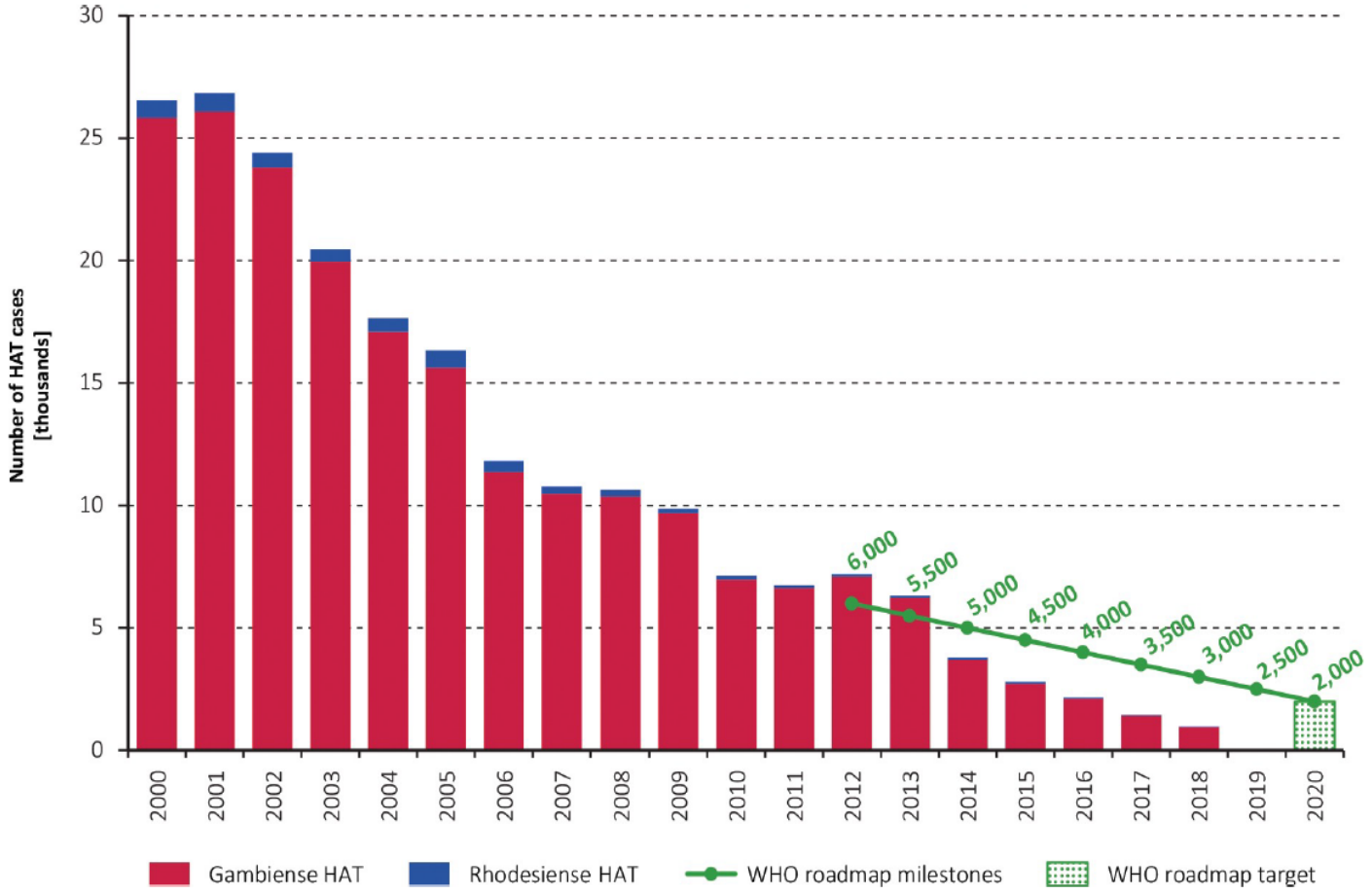
Nagana in cattle

Historical trend of gambiense HAT and screening



Hasker E et al. *Curr Op Infect Dis* 2022

Epidemiology of HAT and WHO target



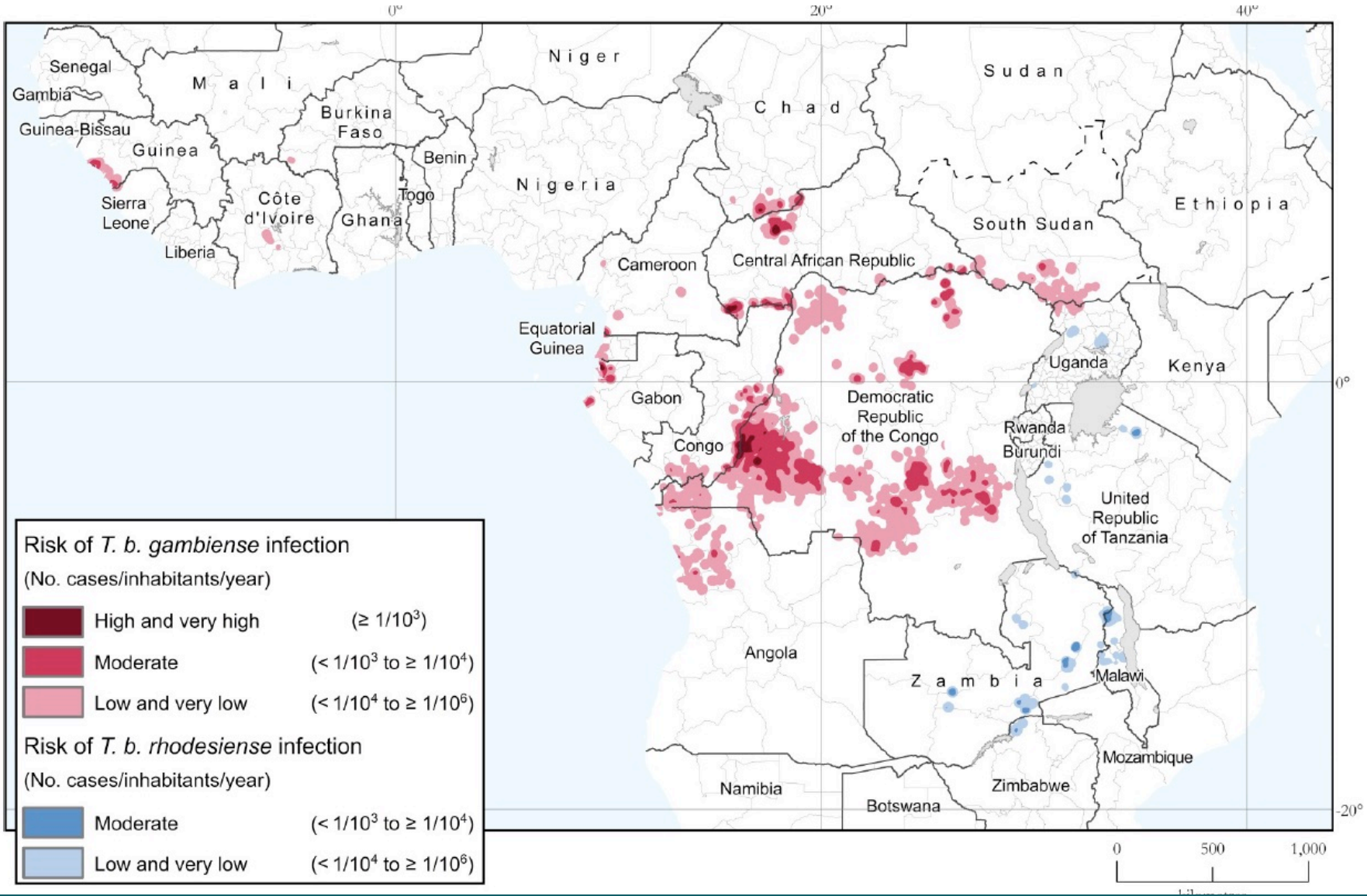
Global:
2018: 953
2019: 876
2020: 565

DRC:
2018: 660
2019: 613
2020: 395

WHO roadmap: g-HAT targeted for elimination (interruption of transmission)	2020	<2000 cases
	2030	Zero cases

Franco JR et al. *PLoS NTD* 2020

Shrinking of risk areas for HAT (update 2018)



Franco JR et al. *PLoS NTD* 2020

Clinical features HAT

T. b. gambiense

- (trypanosomal chancre)

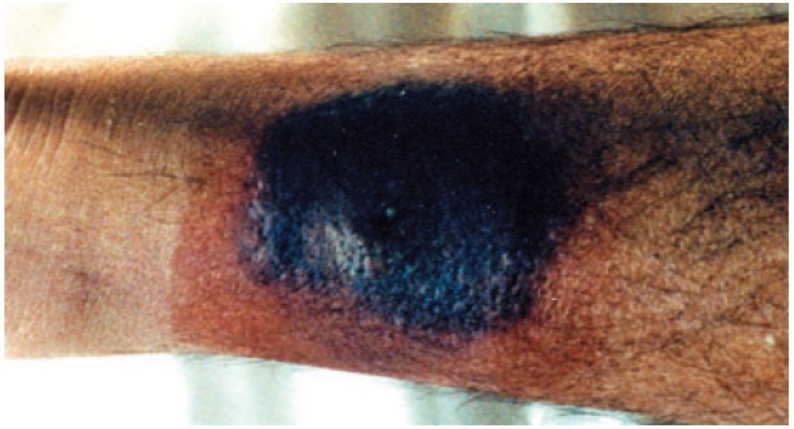
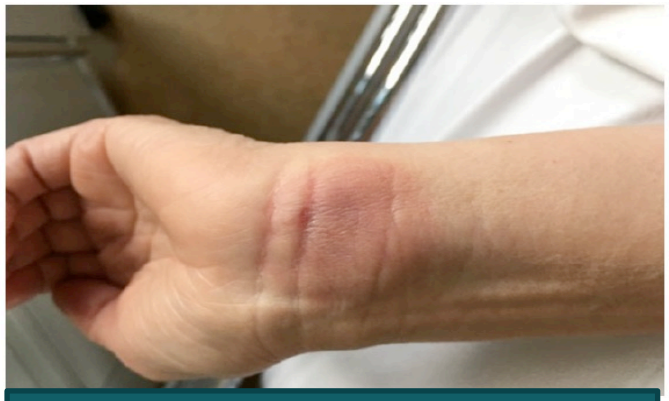


FIG. 3. Trypanosomal chancre on the dorsal side of the right ankle in a 53-year-old French expatriate with *Trypanosoma brucei gambiense* infection.

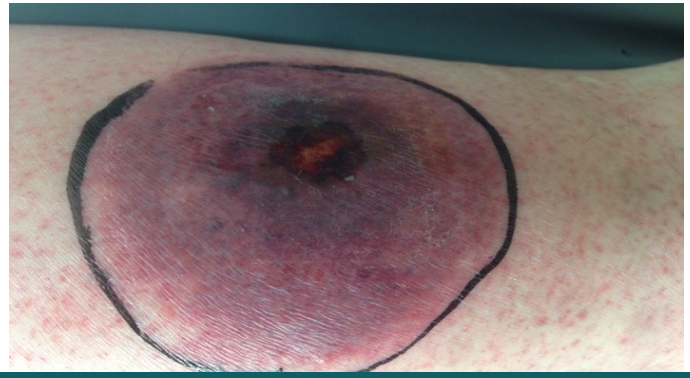
Malvy D *Clin Microbiol Infect* 2011

T. b. rhodesiense

- trypanosomal chancre ++



Wijsman CA *J Travel Med* 2018

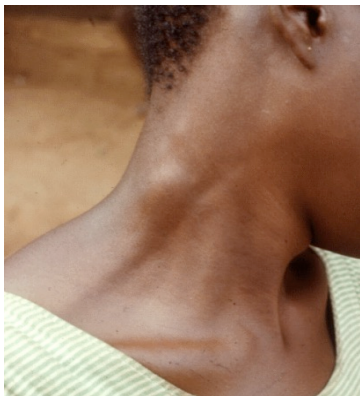


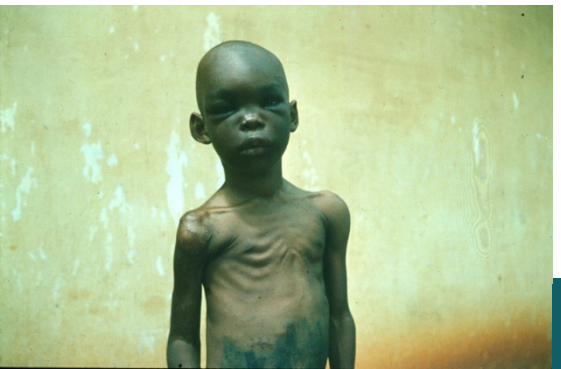
Huits R *J Travel Med* 2018

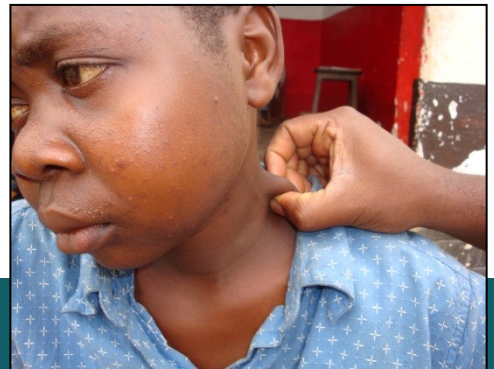
Clinical features HAT

T. b. gambiense

- (trypanosomal chancre)
- hemo-lymphatic stage (first, early)

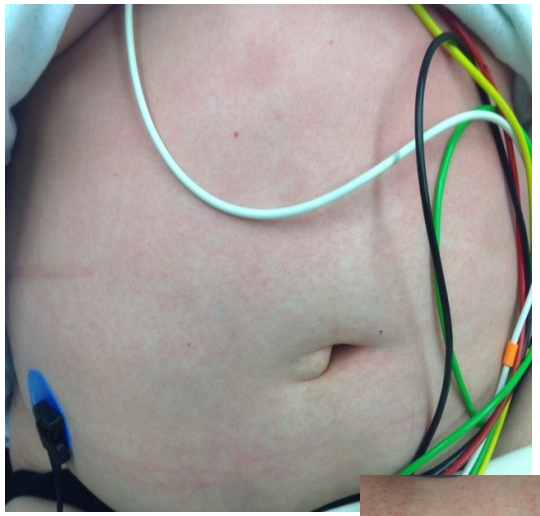


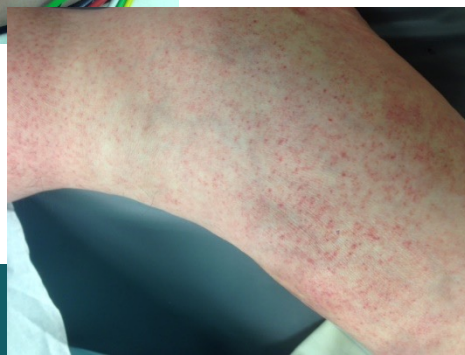




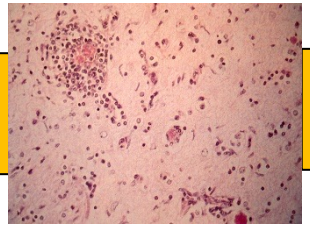
T. b. rhodesiense

- trypanosomal chancre ++
- hemo-lymphatic stage (first, early)





Clinical features HAT

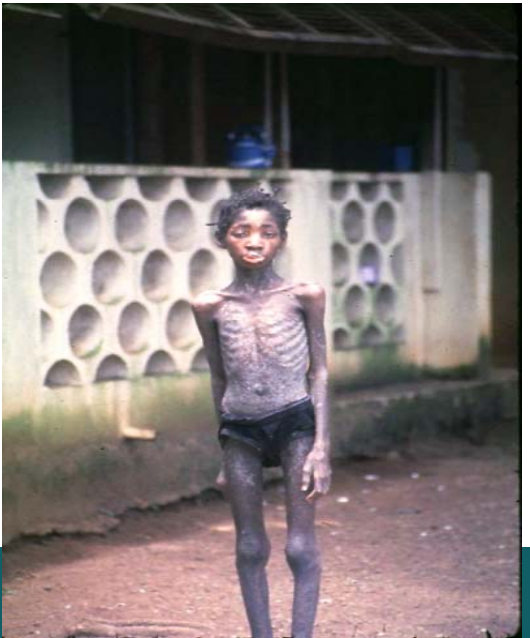


T. b. gambiense

- (trypanosomal chancre)
- hemo-lymphatic stage (first, early)
- meningo-encephalitic stage (second, late)

T. b. rhodesiense

- trypanosomal chancre ++
- hemo-lymphatic stage (first, early)
- meningo-encephalitic stage (second, late)



Clinical features HAT, summary

Table 1
Approximate frequencies (%) of clinical and laboratory features (when available) per disease stage in the main series of human African trypanosomiasis in endemic areas and in travelers

Clinical and Laboratory Features	First-Stage *T.b. gambiense* HAT	Second-Stage *T.b. gambiense* HAT	First-Stage *T.b. rhodesiense* HAT	First-Stage *T.b. rhodesiense* HAT	Second-Stage *T.b. rhodesiense* HAT
N evaluated	39[29] + 56[30]	2541[31]	83[38]	45[36]	138[39] +192[38]
Setting	Endemic	Endemic	Endemic	Travelers	Endemic
Non-neurological features					
Chancre	<5	0	50	85	15
Documented fever	20	15	50	100	20
Headache	80	80	70	50	95
Anorexia	—	25	—	—	85
Pruritus	45	50	—	5	20
			50	40	30
			25	—	40
			—	25	—
Skin rash	—	—	—	30	—
Splenomegaly	50	15	15	25	25
Neurologic features					
Any sleeping disorder	60	75	25	10	85
Daytime sleeping	—	40	25	5	75
Insomnia	—	55			
Behavior change	10	30			
Motor weakness	—	35			
Walking difficulties	—	20			
Altered consciousness	—	15	5	<5	20
Sensory-motor deficit	—	35	—	—	20
Tremor	—	20	30	5	40
Abnormal movements	15	10	—	<5	25
Speech impairment	—	15	—	—	15
Laboratory findings					
CSF-WBC 6–19/μL	—	22	—	—	25
CSF-WBC 20–99/μL	—	32	—	—	38
CSF-WBC >100/μL	—	45	—	—	37
Trypanosomes in CSF	—	40	—	—	85
Trypanosomes in blood	30–75	30–75	95	95	95

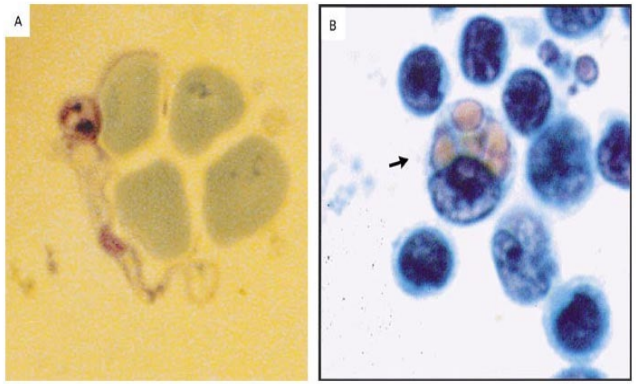
Trypanosoma brucei gambiense Human African Trypanosomiasis Mainly Presents as a Slow-Progressing Neurologic Disease

Trypanosoma brucei rhodesiense Human African Trypanosomiasis Is Mainly an Acute Systemic Febrile Illness

Bottieau E. *Infect Dis Clin N Am* 2019

T. b. gambiense & T. b. rhodesiense, staging

- Need of cerebrospinal fluid (CSF) examination
- Criteria for diagnosis of meningo-encephalitic stage:
  - **Presence of tryps in CSF**
  - **Presence of > 5 leukocytes/µL**
  - (Proteinorachy > 370 mg/L)
  - (Presence of Mott cells)



Not systematically recommended any more ?

Diagnosis of HAT

T. b. gambiense

- Serological
  - field assays
  - (reference assays)

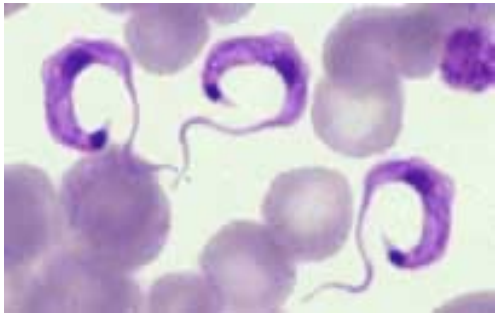
Screening

- Parasitological
  - Blood smear (thick/thin drop)
  - Lymph node aspiration
  - Blood concentration methods
  - (Cerebrospinal fluid; CSF)

Confirmation

T. b. rhodesiense

- Parasitological

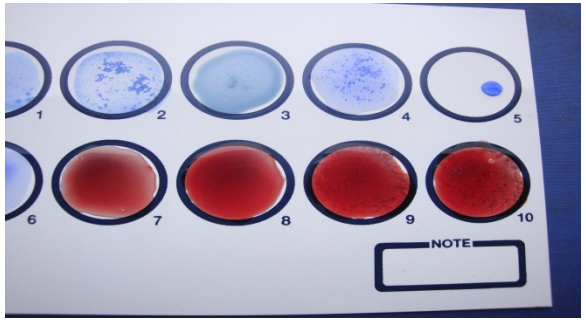


High sensitivity of blood smear examination (sufficient)

Diagnosis of gambiense-HAT: serology

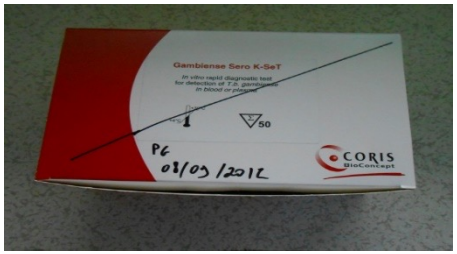
Sens | Spec

- **Screening (field)**
  - Card Agglutination Trypanosoma Test (CATT)



95% | 95%

  - Lateral-flow immunochromatographic assays



95% | 95%

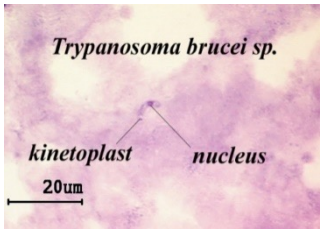
- **Reference (central laboratory)**
  - Trypanolysis; ELISA;...

Chappuis et al. *Clin Microbiol Rev* 2005; Mitashi et al. *PLoS NTD* 2012

Diagnosis of gambiense-HAT: parasitology

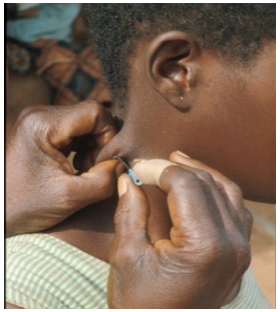
Sensitivity

- Blood (thick/thin drop)



25-30%

- Lymph node aspiration



40%

- Concentration methods
  - Microhematocrit centrifugation technique (mHCT or Woo)

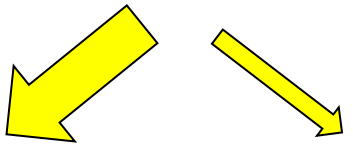
60%

  - Mini-Anion Exchange Centrifugation Technique (mAECT)

85%

Chappuis et al. *Clin Microbiol Rev* 2005; Mitashi et al. *PLoS NTD* 2012

HAT in the non-endemic setting 2000-2010 (n=94)



T.b. rhodesiense HAT (72%)

- Almost exclusively tourists
- From Tanzania (59%), Malawi (19%), Zambia (12%),
- 97% diagnosed by blood smear
- 88% diagnosed in stage 1
- Within 1-3 weeks after exposure
- Diagnostic delay 1-7 days

T.b. gambiense HAT (28%)

- Mostly migrants
- From DRC (23%), Gabon (23%), Angola (15%)
- 39% diagnosed by blood smear
- 77% diagnosed in stage 2
- Diagnostic delay 3-12 months

Simarro et al. *J Travel Med* 2012

Treatment of HAT:

Older drugs

- Pentamidine IV
- Suramin IV
- Melarsoprol IV
- Eflornithine IV
- (Nifurtimox PO)

Depends on:

-trypanosoma species
-disease stage

Novel drugs

DNDi
Drugs for Neglected Diseases *initiative*

- Fexinidazole
  - 10-day, PO
- Acoziborole
  - Single-dose, PO

Pan-species?

Pan-stage?

-

T. b. gambiense HAT second stage: NECT

Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial

Gerardo Priotto, Serena Kasparian, Wilfried Mutombo, Daniel Ngouama, Sara Ghorashian, Ute Arnold, Salah Ghabri, Elisabeth Baudin, Vincent Buard, Serge Kazadi-Kyanza, Médard Ilunga, Willy Mutangala, Gabriele Pohlig, Caecilia Schmid, Unni Karunakara, Els Torreele, Victor Kande

NECT is

- non-inferior than eflornithine monotherapy
- easier to administer
- less expensive
- as safe as eflornithine and less toxic than melarsoprol
- has been proven safe also in phase 4 studies

Priotto G et al. *Lancet* 2009; Alirol et al. *Clin Infect Dis* 2012

New therapeutic developments

DNDi
Drugs for Neglected Diseases *initiative*

Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial

Victor Kande Betu Ku Mesu, Wilfried Mutombo Kalonji, Clélia Bardonneau, Olaf Valverde Mordt, Séverine Blesson, François Simon, Sophie Delhomme, Sonja Bernhard, Willy Kuziena, Jean-Pierre Fina Lubaki, Steven Lumeya Vuvu, Pathou Nganzobo Ngima, Hélène Mahenzi Mbembo, Médard Ilunga, Augustin Kasongo Bonama, Josué Amici Heradi, Jean Louis Lumaliza Solomo, Guylain Mandula, Lewis Kaninda Badibabi, Francis Regongbenga Dama, Papy Kavunga Lukula, Digas Ngolo Tete, Crispin Lumbala, Bruno Scherrer, Nathalie Strub-Wourgaft, Antoine Tarral

Lancet 2018; 391: 144-54

Summary

Background Few therapeutic options are available to treat the late-stage of human African trypanosomiasis, a neglected

Fexinidazole (n=264) vs NECT (n=130)

- Similar efficacy: 91% vs 98%
- Similar mortality: 3% vs 2%

Non-inferior treatment for *T.b. gambiense* HAT stage 1 and 2

However...

Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial

Victor Kande Betu Ku Mesu, Wilfried Mutombo Kalonji, Clélia Bardonneau, Olaf Valverde Mordt, Séverine Blesson, François Simon, Sophie Delhomme, Sonja Bernhard, Willy Kuziena, Jean-Pierre Fina Lubaki, Steven Lumeya Vuvu, Pathou Nganzobo Ngima, Hélène Mahenzi Mbembo, Médard Ilunga, Augustin Kasongo Bonama, Josué Amici Heradi, Jean Louis Lumaliza Solomo, Guylain Mandula, Lewis Kaninda Badibabi, Francis Regongbenga Dama, Papy Kavunga Lukula, Digas Ngolo Tete, Crispin Lumbala, Bruno Scherrer, Nathalie Strub-Wourgaft, Antoine Tarral

Lancet 2018; 391: 144-54

Summary

Background Few therapeutic options are available to treat the late-stage of human African trypanosomiasis, a neglected

Fexinidazole efficacy in patients with > 100 WBC vs < 100 WBC/µL in CSF:
87% vs 99%

Inferior to NECT for “advanced” gambiense-HAT second-stage

Treatment of gambiense-HAT, recent development

Safety and efficacy of oral fexinidazole in children with gambiense human African trypanosomiasis: a multicentre, single-arm, open-label, phase 2–3 trial

Victor Kande Betu Kumesu, Wilfried Mutombo Kalonji, Clélia Bardonneau, Olaf Valverde Mordt, Digas Ngolo Tete, Séverine Blesson, François Simon, Sophie Delhomme, Sonja Bernhard, Pathou Nganzobo Ngima, Hélène Mahenzi Mbembo, Jean-Pierre Fina Lubaki, Steven Lumeya Vuvu, Willy Kuziena Mindele, Médard Ilunga Wa Kyhi, Guylain Mandula Mokenge, Lewis Kaninda Badibabi, Augustin Kasongo Bonama, Papy Kavunga Lukula, Crispin Lumbala, Bruno Scherrer, Nathalie Strub-Wourgaft, Antoine Tarral

Summary

Background Fexinidazole has been reported as an effective oral monotherapy against non-severe gambiense human African trypanosomiasis in a recent trial in adults. We aimed to assess the safety and efficacy of fexinidazole in children across all disease stages of gambiense human African trypanosomiasis.

Lancet Glob Health 2022; 10: e1665–74

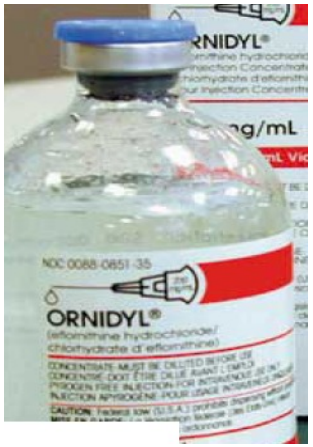
Published Online September 27, 2022

10-day fexinidazole is safe and effective (>95%) for first- and early and late second-stage gHAT in children < 6 years
(Betu Kumesu VK *Lancet Glob Health* 2022)

Treatment of gambiense-HAT, first-stage

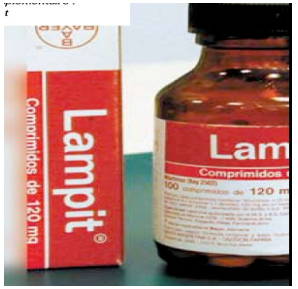
Up to now	Pentamidine IM or IV 4mg/kg OD for 7 days
Now	Fexinidazole PO OD for 10 days

Treatment of gambiense-HAT, second-stage



Up to now

NECT (since 2015)
Eflornithine IV 2 x 200 mg/kg for 7 days
+ Nifurtimox PO 15 mg/kg tid for 10 days



Now

Fexinidazole PO OD for 10 days

Except if advanced disease/presence of > 100 WBC/µL in CSF,
where NECT is still preferred

Third choice

Eflornithine slow IV 4 x 100 mg/kg 14 days

Treatment of gambiense-HAT, recent development

Efficacy and safety of acoziborole in patients with human African trypanosomiasis caused by *Trypanosoma brucei gambiense*: a multicentre, open-label, single-arm, phase 2/3 trial

Victor Kande Betu Kumeso, Wilfried Mutombo Kalonji, Sandra Rembry, Olaf Valverde Mordt, Digas Ngolo Tete, Adeline Prêtre, Sophie Delhomme, Médard Ilunga Wa Kyhi, Mamadou Camara, Julie Catusse, Stefan Schneitter, Morgane Nusbaumer, Erick Mwamba Miaka, Hélène Mahenzi Mbembo, Joseph Makaya Mayawula, Mariame Layba Camara, Félix Akwaso Massa, Lewis Kaninda Badibabi, Augustin Kasongo Bonama, Papy Kavunga Lukula, Sylvain Mutanda Kalonji, Phyll Mariero Philemon, Ricardo Mokilifi Nganyonyi, Hugues Embana Mankiara, André Asuka Akongo Nguba, Vincent Kobo Muanza, Ernest Mulenge Nasandhel, Aimée Fifi Nzeza Bambuwu, Bruno Scherrer, Nathalie Strub-Wourgaft, Antoine Tarral

Summary

Background Human African trypanosomiasis caused by *Trypanosoma brucei gambiense* (gambiense HAT) in patients with late-stage disease requires hospital admission to receive nifurtimox–eflornithine combination therapy (NECT). Fexinidazole, the latest treatment that has been recommended by WHO, also requires systematic admission to hospital, which is problematic in areas with few health-care resources. We aim to assess the safety and efficacy of acoziborole in adult and adolescent patients with gambiense HAT.

Lancet Infect Dis 2022
Published Online
November 29, 2022
https://doi.org/10.1016/
S1473-3099(22)00660-0

Single-dose acoziborole is safe and effective in early and late second-stage gHAT in patients > 15 years
(Betu Kumesu VK *Lancet Infect Dis* 2022)

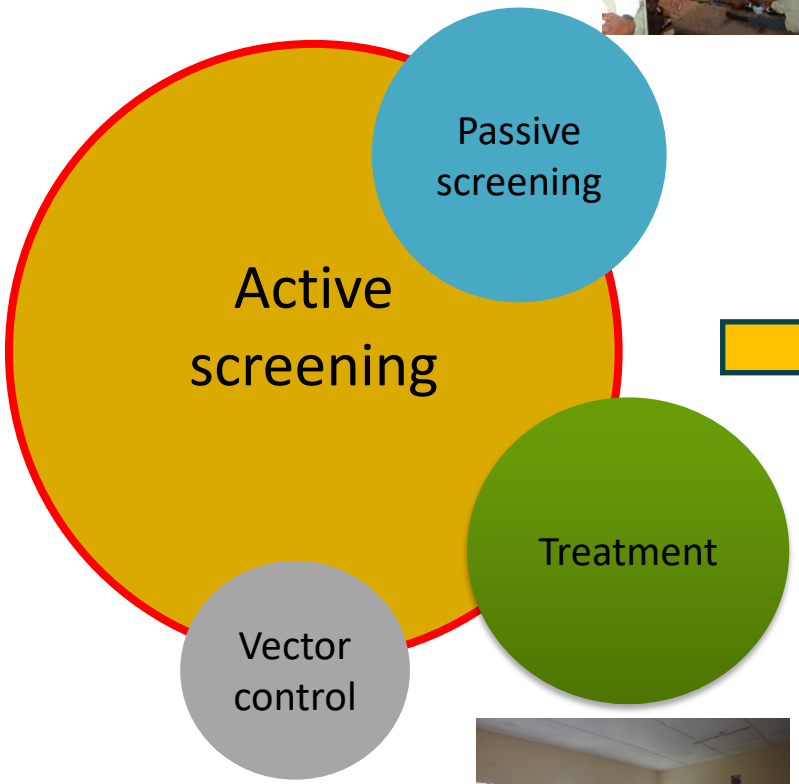
T.b. rhodesiense HAT: treatment

First-stage	Suramin (1 gr/week for 5 weeks)
Second-stage	(Suramin) + Melarsoprol (2.2 mg/kg/d 10 days) + Prednisolone

Fexinidazole PO OD for 10 days ?

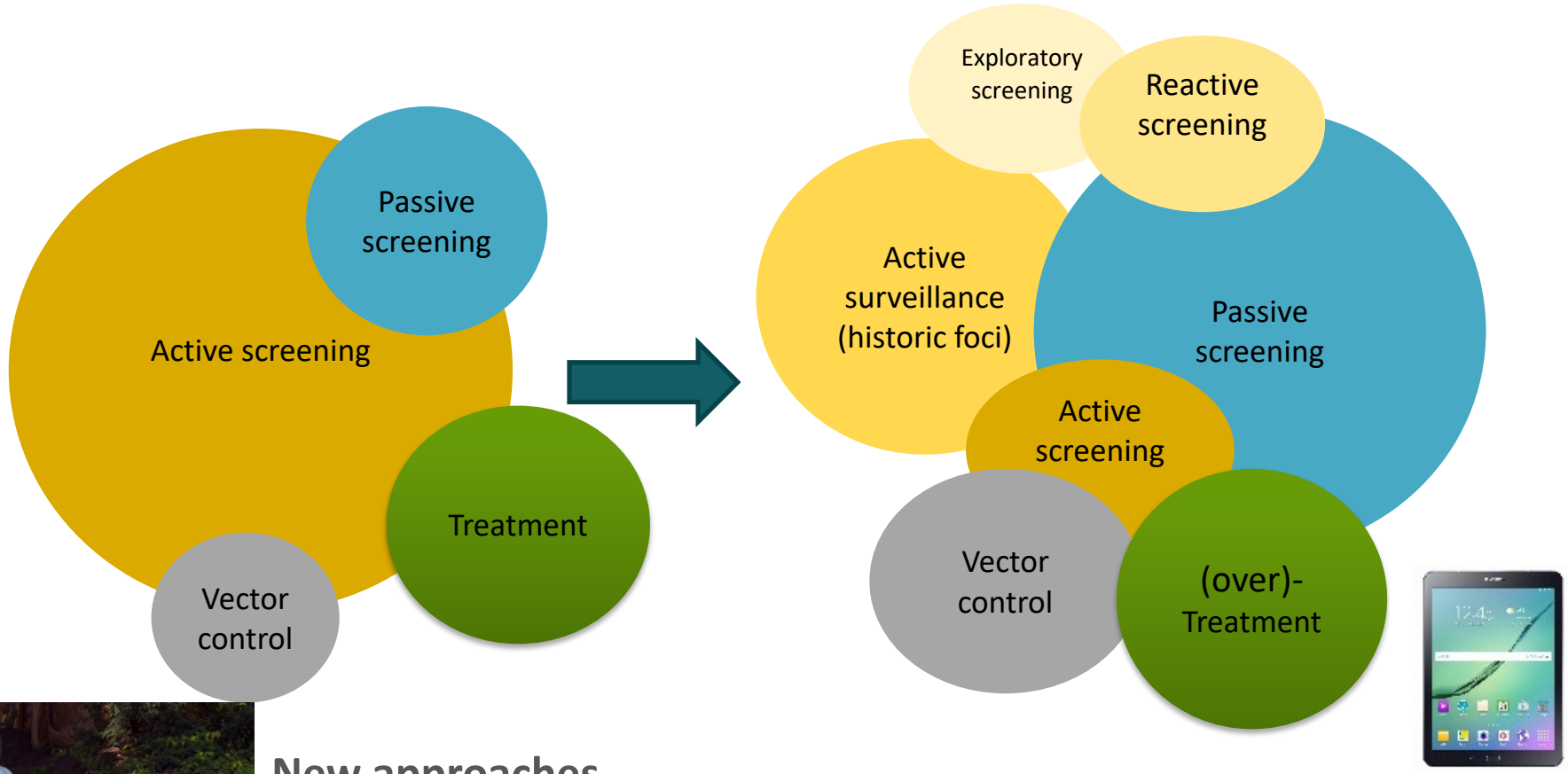
Trial completed; publication pending

Control of HAT - Past strategy



CATT

Control of HAT - New strategy



New approaches

- Reduced active rounds (up to 3 years after last case)
- Screen/confirm/(stage)/treat
- Smaller flexible mobile teams (mapping)

HAT 2023: conclusions

- Historic low numbers of g-HAT cases / sporadic r-HAT cases
- Chronic neurological disease (g-HAT) vs acute systemic illness (r-HAT)
- Improvement of field diagnostics for g-HAT
- Major progress for g-HAT, with oral 10-day fexinidazole (down to oral single-dose acoziborole?); stagnation for r-HAT treatment
- Innovative control approaches for g-HAT
- HAT elimination in 2030 ?
  - Challenges ahead: historic foci; asymptomatic carrier; animal reservoir?

Merci pour votre attention