

Human African trypanosomiasis

Büscher Philippe PhD^{§1}, Cecchi Giuliano PhD², Jamonneau Vincent PhD³, Priotto Gerardo MD⁴

¹ Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

² Food and Agriculture Organization of the United Nations, Sub-regional Office for Eastern Africa, Addis Ababa, Ethiopia

³ UMR INTERTRYP, Institut de Recherche pour le Développement, Montpellier, France

⁴ World Health Organization, Control of Neglected Tropical Diseases, Innovative and Intensified Disease Management, Geneva, Switzerland

[§]Corresponding author: Philippe Büscher (pbuscher@itg.be), +32 3 247 63 71

Email addresses:

PB: pbuscher@itg.be

GC: giuliano.cecchi@fao.org

VJ: vincent.jamonneau@ird.fr

GP: priottog@who.int.

Abstract

Human African trypanosomiasis (HAT), also called sleeping sickness, is a parasitic infection that almost invariably progresses to death, unless treatment is provided. HAT caused devastating epidemics during the 20th century. Thanks to sustained and coordinated efforts during the past 15 years the number of reported cases has fallen to a historic low. Fewer than 3,000 cases were reported in 2015, and the disease is targeted for elimination by the World Health Organization. Despite recent success, HAT still poses a heavy burden on the rural communities where this highly focal disease occurs, most notably in Central Africa. Since patients are also reported from non-endemic countries outside Africa, HAT should be considered in differential diagnosis for all travellers, tourists, migrants and expatriates who have visited or lived in endemic areas. In the absence of a vaccine, disease control relies on case detection and treatment, and vector control. Available drugs are sub-optimal, but ongoing clinical trials give hope for safer and simpler treatments.

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Introduction

Human African trypanosomiasis (HAT) is a neglected tropical disease that occurs in sub-Saharan Africa, within the distributional limits of the tsetse fly vector. Two forms of the disease exist. The slow-progressing form, caused by *Trypanosoma brucei gambiense*, is found in Western and Central Africa. The faster progressing form, caused by *T. b. rhodesiense*, is found in Eastern and Southern Africa¹.

Since the beginning of the 20th century, HAT has killed millions of people. Today, despite an incomplete arsenal of control tools, but thanks to their large scale and efficient deployment, HAT has become a rare disease. Yet, HAT is still reported from more than 20 countries in Africa where it causes substantial morbidity among the affected rural populations, and it continues to pose the threat of severe epidemics². Furthermore, in a globalised world, HAT cases are diagnosed outside African endemic countries among travellers, tourists, expatriates and migrants³.

Epidemiology

The trypanosomes causing HAT are classically transmitted by the bite of blood sucking tsetse flies (Diptera, genus *Glossina*). *T. b. gambiense* can also be transmitted congenitally⁴⁻⁶. Other routes of transmission are possible but poorly documented and considered extremely rare (sexual, laboratory accidents, blood transfusion, organ transplantation)⁶⁻⁹.

In the early 20th century, devastating epidemics were probably triggered by the ecological disruptions and forced population movements brought about by colonialism¹⁰. Since then, the intensity of control efforts and disease transmission have always been closely linked. In some endemic areas, changes in land use and climate dramatically reduced tsetse populations and interrupted HAT transmission¹¹. Neglecting HAT, either because of social or political instability or because of the tyranny of success, inevitably leads to resurgence. The last alarming peak in HAT transmission occurred in the late 1990s, and it was only brought under control by robust and coordinated efforts.

In 2015, 2804 cases were reported to WHO, of which 2733 were *gambiense* HAT (a 90% reduction since 1999) and 71 were *rhodesiense* HAT (89% reduction). This includes cases diagnosed in both endemic and non-endemic countries. The bulk of the *gambiense* HAT case load continues to be in the Democratic Republic of the Congo (DRC, 86% of cases) followed by the Central African Republic and Chad (5 and 2 % respectively), the only 3 countries reporting more than 50 cases per year. However, in other countries like Sudan and Guinea, under-detection of HAT cases due to respectively civil unrest and an ebola fever outbreak, is to be taken into account. The case load of *rhodesiense* HAT is concentrated in Malawi and Uganda with 82% of cases (http://www.who.int/trypanosomiasis_african/country/en/).

While animal African trypanosomiasis (AAT) or nagana, is widespread in all tsetse infested areas, HAT is characterised by a markedly focal distribution (FIGURE 1)^{1,13}. This patchy distribution is the result of very complex parasite/vector/host/environment interactions, which yet remain to be fully understood. The disease is typically found in rural areas with suitable habitats for the tsetse fly vector and frequent human-tsetse contact. Peri-urban areas can also be affected, especially where riverine tsetse species have adapted to anthropic environments¹⁴⁻¹⁶. People can be infected while farming, fishing, hunting, collecting water or wood, or engaging in any other activity that exposes them to the bite of an infective tsetse fly. All age groups and both sexes are at risk, although prevalence is higher in adults and sex distribution varies in relation to gender-specific at-risk activities (e.g. predominantly-male hunting and fishing or predominantly-female water fetching and small crop growing).

For *gambiense* HAT, humans are believed to constitute the main reservoir. Domestic and wild animals can host *T. b. gambiense*, but their epidemiological role remains unclear¹⁷. For

rhodesiense HAT, infection rapidly leads to death in humans, whilst domestic and wild animals are the main reservoir.

Exported cases of HAT are reported from all continents³. Most are *rhodesiense* HAT cases and concern tourists visiting national parks and game reserves in Tanzania, but also in Kenya, Malawi, Uganda, Zambia and Zimbabwe. Exported cases of *gambiense* HAT are rarer, and they include migrants, refugees and long-term expatriates. Exceptionally long periods (up to three decades, and possibly more) can separate infection from diagnosis^{18,19} so *gambiense* HAT should be considered in differential diagnosis in all people who have ever lived in endemic countries.

Parasite and vector

T. brucei belongs to the *Trypanosomatidae*, a family consisting of exclusively parasitic organisms found world-wide in vertebrates and insects²⁰. These unicellular parasites have co-evolved with their hosts to such an extent that most of them are commensal rather than pathogenic²¹. The species *T. brucei* includes three morphologically indistinguishable subspecies (FIGURE 2). *T. b. brucei*, which causes AAT, is not infective to humans. *T. b. rhodesiense* and *T. b. gambiense* can infect humans as they developed the ability to resist apolipoprotein A (ApoL1), a serum protein that triggers death in other trypanosomes^{22,23}. *T. brucei* cells contain one central nucleus, one single mitochondrion with its own DNA comprising the kinetoplast situated at the posterior end of the cell, and a flagellum attached to the cell by an undulating membrane. During its life cycle (FIGURE 3), alternating between a mammal and an insect (tsetse fly) host, *T. brucei* remains extracellular and undergoes important metabolic adaptations reflected by morphological changes. In the blood and tissues of mammals, trypanosomes can be observed as spindle shaped cells, 20-30 µm long (about 3x the diameter of a human erythrocyte), 2-5 µm wide and characterised by their wriggling movement. Sometimes, shorter forms can also be seen which are metabolically pre-adapted to survival in the tsetse intestines (FIGURE 4). In the mammalian host, the trypanosome cell membrane is covered by a dense coat of identical glycoprotein dimers shielding the underlying membrane against innate immunological attacks, e.g. by complement. These highly immunogenic glycoproteins induce a specific antibody response that triggers destruction of all the trypanosomes opsonised with these antibodies. To survive this antibody mediated immune response, trypanosomes developed "antigenic variation", by which the glycoprotein coat on the cell membrane is replaced by an antigenically different coat²⁴. The interplay between immune response of the host and antigenic variation of the parasite results in irregular fluctuations in parasitaemia, reflected by irregular fevers accompanying destruction of trypanosomes. *T. brucei* infection typically induces a polyclonal B-cell activation resulting in extremely high IgM concentrations (up to 14x normal values) and a variety of non-trypanosome specific antibodies including auto-antibodies. These take part in the pathogenesis of the infection and cause non-specific reactions in antibody detection tests for other infections²⁵⁻²⁷. Infection of mammalian hosts starts with the injection of metacyclic trypanosomes, together with tsetse saliva, into the skin (FIGURE 2). After several days of local multiplication, the trypanosomes spread via the lymph and blood to a variety of peripheral organs and tissues. Later on, the parasites invade the brain parenchyma where they trigger local inflammation and neurological damage²⁸. The parasites' journey through the mammalian host is accompanied and regulated by important immunological reactions, some of which are pathogenic, induced by components of the parasite and the tsetse fly saliva²⁹. For its cyclical transmission, *T. brucei* depends on tsetse flies (<https://vimeo.com/200798320>, courtesy of Jan Van Den Abbeele, ITM). Both sexes are haematophagous and can transmit trypanosomes. Tsetse are viviparous, and the female deposits a fully developed larva that

burrows into the soil, pupates, and emerges as an adult fly a month later. According to morphological differences and habitat preference, the thirty one tsetse species and subspecies are classified as forest, riverine or savannah type³⁰. *G. fuscipes* and *G. palpalis* (from the palpalis riverine group) are the main vectors of *gambiense* HAT^{31,32}. For *rhodesiense* HAT, the main vectors are *G. f. fuscipes* (in Uganda) as well as savannah group species such as *G. morsitans* and *G. pallidipes*^{33,34}. Tsetse flies become infected with *T. brucei* when they ingest trypanosomes residing in the blood or, as shown in experimental infections, in the skin of mammals^{35,36}. Once ingested, the short stumpy trypanosomes undertake a complex journey through the fly tissues, until they reach the salivary glands and develop into the human-infective metacyclic forms³⁷. Under natural conditions, only a small fraction of the tsetse flies carry mature infection of *T. brucei* (about 0.01 %, ^{38,39}) but one single tsetse fly, feeding every 3 days, is able to infect several persons during its two- to three-month life-span. Eliminating the tsetse or reducing tsetse/human contact is one way to reduce or interrupt HAT transmission.

Clinical features

The clinical manifestations of HAT depend on the parasite subspecies, host response and disease stage. Variations of virulence and pathogenicity have been attributed to different parasite strains^{40,41}. Both forms of the disease generally lead to death if untreated, although healthy carriers and self-cure have been described for *gambiense* HAT⁴². *Rhodesiense* HAT is typically acute, progressing to second stage within a few weeks and to death within 6 months^{43,44}. *Gambiense* HAT follows a chronic progressive course, with a mean duration estimated at 3 years, albeit with high interpersonal variability⁴⁵.

The disease goes through two stages, a first, hemo-lymphatic stage followed by a second, meningo-encephalitic stage when trypanosomes cross the blood-brain barrier and invade the central nervous system (CNS). Neurological disturbances, including sleep disorder, are typical of the second stage; however, most signs and symptoms are common to the two stages.

A 3-4 cm dermal reaction at the site of the tsetse bite (inoculation chancre) appears 2-3 days after the bite in between 5 and 26% of native *rhodesiense* HAT patients but is rarely seen in *gambiense* HAT^{40,46}.

First stage *gambiense* HAT presents predominantly with long-lasting intermittent fever (1 day to 1 week, separated by intervals of days or months), headache, pruritus, and lymphadenopathy (mainly posterior cervical, but also possible in the axillar, inguinal and epitrochlear regions). Less frequent features are hepatosplenomegaly, edema and endocrine dysfunction (amenorrhea, infertility, miscarriage in women; reduced libido, impotence in men).

In the second stage, neuropsychiatric disorders add to the first-stage features, while fever becomes less frequent. The characteristic sleep disorder, which elicited the name *sleeping sickness*, consists of daytime somnolence plus sudden overwhelming sleep urges, and nocturnal insomnia. Polysomnographic records show a disruption of the sleep-wake cycle with frequent, short, sleep-onset REM episodes that occur equally during day and night⁴⁷⁻⁴⁹.

Other neurological signs comprise hyper- or hypo-tonicity, tremor of hands and fingers and choreiform, athetoid, or oscillatory movements of limbs or trunk, fasciculation, motor weakness, ataxia, akinesia, and speech disorders. Perioral and cheiro-oral reflexes are frequently seen. Mental changes are common, including emotional lability, attention deficit, indifference, apathy, aggressive behaviour, stereotypic behaviour, dissociative fugue, manic episodes, melancholia, confusion, and dementia. Neuropsychiatric disorders increase with disease progression⁵⁰. Infiltration of endocrine organs (mainly thyroid and adrenals) and the hypothalamic-hypophysial axis lead to disruption of circadian rhythms of hormonal secretion

including prolactin, renin, growth hormone, and cortisol ⁴⁷, but generally do not require specific treatment. Cardiac alterations are common but do not have the clinical relevance they have in Chagas disease (American trypanosomiasis). They develop at early stages of HAT, the main findings being electrocardiogram (ECG) abnormalities including QT-interval prolongation, repolarisation changes, and low voltage, consistent with peri-myocarditis ⁵¹. In *gambiense* HAT these alterations are generally mild, but in *rhodesiense* HAT earlier and more severe peri-myocarditis and congestive cardiac failure are observed ⁵².

The clinical features of *rhodesiense* HAT are similar to those of *gambiense* HAT, but the trypanosomal chancre is more frequent, often with satellite lymphadenopathy. Fever presents in both disease stages and more frequently in children ⁵³. Enlarged lymph nodes tend to be submandibular, axillary and inguinal rather than posterior cervical, and edema is observed more frequently than in *gambiense* HAT. Thyroid dysfunction, adrenal insufficiency and hypogonadism are more common than in *gambiense* HAT, and myocarditis is more severe and even fatal. Liver involvement with hepatomegaly and jaundice are frequent but usually moderate, sometimes with ascitis ⁵⁴. In South-East African countries, in particular Malawi, a more chronic form has been reported, with a lengthier first stage showing fewer neurological disorders and absence of chancre ⁴⁰.

In travellers from non-endemic countries, the incubation period is shorter (< 3 weeks for *rhodesiense* HAT and < 1 month for *gambiense* HAT) and the clinical picture is acute and febrile from the onset, regardless of the subspecies. A trypanosomal chancre is seen more frequently (88% in *rhodesiense* HAT and 56% in *gambiense* HAT) and a rash may appear in one third of the cases, consisting of non-itching, irregular erythematous macules of up to 10 cm, of which many develop a central area of normal coloured skin ⁵⁵. The rash may last several weeks, vanishing and reappearing in different areas ⁵⁶. Headache, lymphadenopathy, hepatomegaly and splenomegaly occur in a quarter to half of patients. In travellers with *rhodesiense* HAT, gastrointestinal symptoms are more frequent, jaundice has been reported in 28% of cases, and less frequent but severe complications include renal failure requiring haemodialysis, multi-organ failure, disseminated intravascular coagulopathy and coma ^{3,57}.

Diagnosis

Clinical signs and symptoms of HAT are unspecific and easily mistaken with those of other diseases. They can thus be suggestive of HAT but are insufficient for diagnosis.

Reliable serodiagnostic tests exist only for *gambiense* HAT and are based on detection of specific antibodies. The Card Agglutination Test for Trypanosomiasis (CATT, ⁵⁸), developed almost 40 years ago, has been pivotal in the control of *gambiense* HAT. CATT can be performed with finger prick blood, plasma or serum and the agglutination reaction is scored visually after 5 minutes. It is particularly suited for screening populations at risk by mobile teams. Its sensitivity is higher in Western than in Central Africa ⁵⁹.

Recently, rapid diagnostic tests (RDT) for *gambiense* HAT were developed and introduced in the field: the HAT Sero-K-SeT (Coris BioConcept, Belgium) and the SD Bioline HAT 1.0 (Standard Diagnostics, South Korea) ⁶⁰⁻⁶². Their major advantage is that they fully comply with the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria and therefore are more suitable for passive screening and surveillance in fixed health centres that often lack electricity and laboratory infrastructure ^{63,64}. Second generation cassette and strip format RDTs including recombinant antigens are under development ⁶⁵⁻⁶⁷.

Although very useful for screening populations at risk and identifying individuals as probably infected with *T. b. gambiense*, CATT and RDTs are not 100% specific ⁶⁸. Particularly when disease prevalence is low, their positive predictive value (PPV) becomes critically low ⁶⁹. For

example, with a specificity of 98% and a prevalence of 0.1%, PPV is only 4.5%. Currently, in most HAT foci, prevalence is far below 0.1% and serological screening tests yield about 99 false-positive results for every true positive.

Immune trypanolysis (TL) and enzyme linked immunosorbent assay (ELISA) are applicable in laboratory conditions on serum, plasma and dried blood spots (DBS)^{26,68,70,71}. Their high specificity and sensitivity, their applicability on DBS and their adaptability to animal specimens make them excellent tools for large scale surveys, post-elimination monitoring and animal reservoir studies^{72,73}.

For *T. b. rhodesiense*, no field-applicable serodiagnostic test exists. Efforts to develop second generation RDTs that detect both *gambiense* and *rhodesiense* HAT are ongoing, but the risk of cross-reaction with antibodies against non-human infective trypanosomes is ever-present^{65,67}. As *rhodesiense* HAT usually presents with high parasitaemia levels, antibody detection is less relevant³¹. Parasitological confirmation of *gambiense* HAT is achieved by microscopic examination of a lymph node aspirate (<https://vimeo.com/200798186>, courtesy of Epcot Hasker, ITM) or by concentration techniques applied on blood (mini Anion Exchange Centrifugation Technique (mAECT) or micro-hematocrit centrifugation technique (mHCT) (<https://vimeo.com/200798225>) or on CSF (modified single centrifugation technique (MSC)⁷⁴⁻⁷⁸. Importantly, to detect the colourless, motile trypanosome at low magnification (10x10, 16x10 or 10x40), the microscope must be adjusted for maximum light diffraction. The diagnostic sensitivity of these techniques is suboptimal (maximum 90%) although the analytical sensitivity of for example the mAECT is < 50 trypanosomes per ml of blood⁷⁹. For *rhodesiense* HAT, usually presenting with higher parasitaemia, stained blood thin film or thick drop or chancre aspirate can be considered if the more sensitive concentration techniques are not available.

Stage determination, i.e. assessing neurological involvement, relies on the examination of CSF collected by lumbar puncture⁸⁰. Patients with ≤ 5 white blood cells (WBC) per μl and no trypanosomes in the CSF are considered in the first stage; > 5 WBC/ μl or presence of trypanosomes in the CSF define second stage³¹. Other markers for neuroinflammation, e.g. intrathecal IgM and neopterin, have been proposed for improved stage determination. However, their added value is minimal (IgM) or quantification is not currently possible under field conditions (neopterin)^{81,82}.

Molecular diagnosis of HAT, as a surrogate for microscopic parasite detection, has been the subject of numerous investigations but should be interpreted with caution in clinical practice, even for exported cases⁸³. All formats suffer from poor diagnostic accuracy, even for stage determination and post-treatment follow-up, poor reproducibility and incompatibility with diagnostic facilities in HAT endemic countries⁸⁴⁻⁸⁶. In some instances, most notably in the context of HAT elimination, it may be useful to identify the subspecies of *T. brucei*, e.g. in tsetse, in animals but also in humans since atypical infections with animal trypanosomes are possible^{32,87-93}. *Gambiense*- and *rhodesiense*-specific PCRs do exist but they target single copy genes, hence their poor analytical sensitivity^{94,95}.

As diagnosis of HAT is a specialty and techniques are not commonly known, technical assistance and reference testing can be obtained from the two WHO Collaborating Centres for HAT (i.e. the Institute of Tropical Medicine in Antwerp, Belgium, and the *Institut de Recherche pour le Développement* (IRD), based at the *Centre International de Recherche et Développement sur l'Élevage en zones Subhumides* (CIRDES) in Bobo Dioulasso, Burkina Faso (http://www.who.int/trypanosomiasis_african/surveillance/collaborating_network/en/).

Treatment

Five drugs are used in HAT therapy: pentamidine and suramin to treat first-stage, and melarsoprol, eflornithine and nifurtimox for second stage disease. All are donated by the manufacturers, and WHO ensures their worldwide distribution free of charge. Because of this, HAT treatment is not affected by the issue of counterfeit and substandard drugs. The drugs can be obtained directly from WHO in Geneva (priottog@who.int, francoj@who.int) or from a few institutes that keep strategic stocks around the world (Table 1)³.

The earlier HAT is treated, the better the prospects of treatment tolerability and cure. The choice of treatment depends on the causative agent and disease stage (Table 2). Drugs for the first stage will generally not cure a second stage, and second stage drugs are not justified in first stage because of their toxicity and cumbersome logistics. In fact, treatment of second stage requires drugs that cross the blood-brain barrier and such drugs tend to be toxic and complicated to administer.

First stage treatment

Pentamidine: Pentamidine isethionate is the first-line treatment for first-stage gambiense HAT, and is also an alternative for rhodesiense HAT, although data on its efficacy against *rhodesiense* HAT are still limited^{55,96}. Pentamidine efficacy against gambiense HAT (95-98%) has been stable for decades. It is given intramuscularly once a day for 7 days, but can also be given in intravenous infusion in saline over 2 h. Administration should be preceded by sugar ingestion (10-20 gram) to prevent hypoglycaemia, and followed by rest in supine position for 1 to 2 hours to prevent the effects of hypotension. Pentamidine is generally well tolerated. The intramuscular injection causes pain and transient swelling. Other adverse events include hypoglycaemia (5–40%), hypotension, abdominal pain and gastrointestinal problems⁹⁷.

Suramin: Although effective in the first stage of both *gambiense* and *rhodesiense* HAT, suramin is used only in *rhodesiense* HAT because of the risk of onchocerciasis coinfection in *gambiense* HAT endemic areas (i.e. risk of allergic reactions arising from rapid killing of microfilaria), and because pentamidine administration is simpler. Suramin is administered slowly intravenously. It deteriorates rapidly in air and must be injected immediately after dilution. Recommended schedules are complex and last up to one month. A test dose is applied before treatment initiation due to the risk of acute hypersensitivity reactions. Adverse effects are frequent but mostly mild and reversible, including pyrexia, nephrotoxicity, peripheral neuropathy, agranulocytosis and thrombocytopenia.

Second stage treatment

Nifurtimox–eflornithine combination therapy: The first line treatment for second stage *gambiense* HAT is nifurtimox–eflornithine combination therapy (NECT). In 2009 NECT was incorporated in the WHO Essential Medicines List. Compared to melarsoprol or eflornithine monotherapy, NECT has higher cure rates (95-98%), lower fatality rates (<1%), less severe adverse events, simpler administration, and it is believed to avoid drug resistance of the parasite⁹⁸⁻¹⁰¹. Because nifurtimox is not licenced for African trypanosomiasis (only for American trypanosomiasis), nifurtimox can only be used to treat HAT patients off-label, subject to express authorization and responsibility acceptance by national authorities. WHO supplies endemic countries, free of charge, a full NECT kit containing all the drugs and material needed for its administration. NECT consists of oral nifurtimox and intravenous eflornithine. A dose of nifurtimox should be readministered if vomiting occurs within 30 minutes. With 14 infusions instead of 56 with eflornithine monotherapy, NECT is much easier to administer, demanding less hospitalisation resource and reducing costs. Although the short half-life of eflornithine theoretically requires 4 daily infusions for a constant

trypanostatic effect, 12-hourly infusions are highly effective when combined with oral nifurtimox. The most common treatment-emergent adverse events are abdominal pain, vomiting, and headache^{98,99,101-104}. The toxicity profile replicates that of nifurtimox and eflornithine monotherapies, but with lower frequency and severity, most likely due to the shorter drug exposure. NECT is better tolerated in children.

Eflornithine monotherapy: Eflornithine (α -difluoromethylornithine or DFMO) is given in monotherapy for gambiense HAT when nifurtimox is unavailable or contraindicated. It is a cytostatic and trypanostatic drug. Evidence exists that an active immune system is required to achieve cure¹⁰⁵. Eflornithine as monotherapy is given in a slow intravenous infusion for 14 days (56 infusions in total). In resource-poor settings this burdensome schedule is challenging and imposes specific care to prevent catheter-related infections. A 7-day regimen showed insufficient efficacy. A higher dose (600 mg/kg/day) in children <12 years did not improve effectiveness. Eflornithine monotherapy has proved effective against gambiense HAT (90-95% cure rate) but is not recommended for rhodesiense HAT^{98,106,107}. Adverse events are frequent and similar to other cytostatics (including diarrhoea and neutropenia), but eflornithine is on the whole safer than melarsoprol, with fatality rates below 2%^{106,108}. The main adverse events are fever, pruritus, hypertension, nausea, vomiting, diarrhoea, abdominal pain, headaches, myelosuppression (anemia, leucopenia, thrombocytopenia), and, more rarely, seizures that are generally isolated and respond to treatment.

Melarsoprol: Due to the high frequency of severe and life-threatening adverse drug reactions, and the availability of better alternatives, melarsoprol is restricted to treatment of second-stage rhodesiense HAT. In gambiense HAT the only remaining indication is the treatment of relapse after NECT or eflornithine monotherapy. The most important serious reaction is an encephalopathic syndrome that occurs in 5–18% of all treated cases and is fatal in 10–70% of affected patients¹⁰⁹. Both the incidence and fatality rates are higher in rhodesiense than in gambiense HAT. Co-administration of prednisolone may have a protective effect. The syndrome usually occurs between 7 and 14 days after the first injection and is characterised by fever and either convulsions, rapid onset of neurological disorders, progressive coma or abnormal behaviour¹¹⁰. Close monitoring of patients may allow detection of early signs such as fever and/or headache and to stop melarsoprol and institute management with dexamethasone and diazepam¹¹¹. Other frequent adverse reactions include pyrexia, headache, general malaise, gastrointestinal (nausea, vomiting, diarrhoea) and skin reactions (pruritus); severe complications like exfoliative dermatitis occur in < 1% of cases¹¹⁰. Cardiac failure is common and may be fatal but it may be attributable also to HAT itself¹¹².

Drug resistance

Mutations in the genome of *T. b. gambiense* conferring resistance to melarsoprol and pentamidine have been documented. In particular, melarsoprol resistance generated much concern at the turn of the century, when the failure rates rose in several HAT foci^{113,114}. The concern was removed with the introduction of NECT, which combines two drugs of different pharmacodynamics, strongly decreasing the probability of resistance emergence.

Treatment in pregnancy

Although poorly studied, field experience has accumulated on the management of pregnant and lactating patients³¹. Pentamidine can be given after the first trimester of pregnancy. Nifurtimox, eflornithine and melarsoprol, all theoretically contraindicated, in practice are given when the mother is in advanced second stage, and her condition does not permit waiting. If postponing second-stage treatment until childbirth is judged possible, a pentamidine full course should be administered, principally to prevent vertical transmission. The benefits and risks must be clearly explained to the patient and her relatives. In rhodesiense HAT, the acute clinical evolution usually precludes waiting until delivery, and

suramin (also theoretically contraindicated) or melarsoprol are given. New-borns should be examined clinically and checked for the presence of trypanosomes in the blood. Breastfeeding should continue during HAT treatment.

Post-therapeutic follow-up

The assessment of treatment outcome requires following up the patient up to 24 months with laboratory exams of body fluids including cerebrospinal fluid, as parasites may remain viable for long periods and cause relapses. In rural Africa such follow-up plan is challenging and is not done systematically, but patients are advised to consult if symptoms reappear.

New drugs in the pipeline

Two new molecules are currently in clinical development, which could revolutionise HAT treatment, notably because they are administered orally and are intended for treatment of both disease stages, thus eliminating the need for stage determination through an invasive lumbar puncture. Fexinidazole, a nitroimidazole taken orally once a day for 10 days, is in phase II/III trials near conclusion¹¹⁵, and a benzoxaborole called SCYX-7158, taken in one single oral dose has entered a phase II/III trial¹¹⁶.

Epidemiological surveillance

Surveillance is crucial for HAT control because of its focal distribution, occurrence in remote rural areas and capacity to re-emerge when control activities are relaxed. Also, control operations are resource-intensive and therefore require careful targeting. Surveillance is carried out by national HAT control programmes with support from WHO and other partners. Field data are collected through active and passive case detection, and they are assembled, harmonised and geo-referenced at the village level in the Atlas of HAT^{2,117,118}. The Atlas provides maps of disease occurrence, risk levels, control activities, exported cases and health facilities with capacity for HAT diagnosis and treatment^{1,3,119,120}. Such maps provide crucial evidence to plan control activities at national and sub-national level and to monitor the progress towards HAT elimination¹²¹. Importantly, HAT is often under-diagnosed because of limited accuracy of diagnostic methods, insufficient staff capacities, incomplete community participation, and limited access to remote or insecure areas.

Control and elimination

In the absence of a vaccine or chemoprophylaxis, HAT is controlled through case detection and treatment, and, to a lesser extent, vector control.

For *gambiense* HAT, the most effective control strategy is case finding and treatment, which reduces the human reservoir and thus decreases transmission. Cases are detected via active screening campaigns by mobile teams, consisting of up to 8 persons travelling in 4x4 vehicles or boats, and via passive screening in fixed health structures¹²⁰. Diagnosis and treatment are resource-intensive and require specific training, which is difficult to ensure in all countries and all endemic areas. Although active mass screening has saved thousands of lives and led to a sweeping reduction of HAT risk, this labour-intensive strategy is no longer cost-effective in the numerous low-prevalence settings. Moreover, where HAT is no longer perceived as a threat, populations are reluctant to participate in repeated, time-consuming screening activities^{73,122,123}. In low prevalence settings, targeted door-to-door surveys focused on the immediate vicinities of former HAT patients may provide an alternative to mass screening, and complement passive case detection¹²⁴. Active screening can also be performed by "light"

mobile teams consisting of 1 to 2 persons travelling on motorbikes and reaching villages or camps that are inaccessible to 4x4 vehicles ¹²⁵.

In the current elimination context, it is also crucial to reinforce passive surveillance, integrating it in the general healthcare system and focusing on self-presenting patients ^{126,127}.

As passive surveillance relies on clinical suspicion followed by serological tests, it mostly detects second-stage patients, who are likely to have fed the transmission cycle for years before detection ¹²⁸. It is therefore necessary to carry out reactive screening campaigns in the probable areas of infection of these passively-detected patients.

Although vector control in *gambiense* HAT settings has been limited due to the availability of better options, improved tools and strategies such as low-cost small insecticide-treated screens (the so called "tiny targets"), were shown to enhance traditional *gambiense* HAT control in certain epidemiological settings ¹²⁹. Other tsetse control tools such as insecticide treated cattle also exist, which can be very cost effective in the appropriate settings and in a One Health framework ^{130,131}. To date, no insecticide resistance has been reported in tsetse. For *rhodesiense* HAT, control of the domestic animal reservoir is key. Blanket treatment of cattle, the reservoir and amplifier closest to humans, as well as insecticide application on these animals, have been used to contain epidemics ^{132,133}. Other methods include bush clearing, aerial or ground spraying of insecticide, insecticide-impregnated nets and screens, fly traps, and release of sterile male tsetse. Integrating several methods in a combined approach is recommended ¹³⁴. By contrast, effective tools to control the wild animal reservoir are lacking. Travellers to endemic areas may take measures to prevent tsetse bites, such as avoiding specific places known as tsetse habitat, travelling in vehicles with screens or closed windows, wearing clothes with long sleeves and avoiding dark (especially blue and black) colours. Insect repellents provide very limited protection.

In a context of steady progress against HAT (85% reduction in cases reported in the last 16 years) WHO targeted the elimination of the disease as a public health problem by 2020. Beyond that, vulnerabilities in the transmission cycle and the focal distribution of *gambiense* HAT make its interruption possible (WHO target for 2030). By contrast, the interruption of *rhodesiense* HAT transmission does not seem attainable with the available tools. Despite recent advances, the elimination process faces many challenges: (i) sustaining the commitment of national authorities, partners and donors; (ii) overcoming the limitations of the current diagnostic and treatment tools; (iii) integrating HAT control in peripheral health facilities; (iv) reaching populations living in or fleeing from areas of civil unrest; (v) clarifying the role of, and if necessary addressing, the asymptomatic human carriers and the possible animal reservoir for *gambiense* HAT; (vi) further developing tools and criteria to monitor, verify and validate HAT elimination at different geographical scales.

Conclusions

HAT has long been a typical neglected tropical disease, characterised by suboptimal control tools and inadequate funding. Over the last 15 years, thanks to the efforts of a broad range of stakeholders, the situation has completely changed. Today, HAT is a rare disease that is targeted for elimination. Drugs are available for free thanks to donations of the manufacturers, low-cost RDTs and vector control tools are on the market; new safe, oral drugs are expected to become available soon and the integration of HAT diagnosis in peripheral health centres has begun. Yet, HAT control may become the victim of its own success. History teaches us that falling numbers of HAT cases can result in decreased interest of donors and control agencies, thus opening the door to swift and severe recrudescence. Also, the progressive dismantling of highly specialised mobile teams entails the loss of expertise in HAT diagnosis with grave consequences at the individual and community level.

Despite the challenges, if current commitments and coordinated efforts can be sustained, HAT may well become a disease of the past. This will require the continuous provision of drugs, support by financial partners, adequate prioritisation and ownership of HAT elimination at the national level, and coordination of the numerous actors involved in this laudable endeavour.

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Contributors

PB coordinated the drafting of the manuscript. All authors contributed equally to the writing of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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Disclaimer

The boundaries and names shown and the designations used on the maps presented in this paper do not imply the expression of any opinion whatsoever on the part of FAO or WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. The views expressed in this paper are those of the authors and do not necessarily reflect the views of FAO or WHO.

Search strategy and selection criteria

We searched PubMed with the following keywords: "sleeping sickness" or "Trypanosoma brucei gambiense" or "Trypanosoma brucei rhodesiense" or "CATT" or "suramine" or "pentamidine" or "melarsoprol" or "eflornithine" or "tsetse" or "Glossina" or "human African trypanosomiasis" and limited to publications between 2010 and present. Among the almost 3000 references, we selected those we judged relevant, prioritising those reporting applied research. An additional source was the Programme against African Trypanosomosis (PAAT) Tsetse & Trypanosomosis Information Bulletin (2010–2015), edited by FAO. Additional references were retrieved from the personal databases of all co-authors.

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BOX 1: RESEARCH PRIORITIES

Treatment: Whilst there is hope for two safer drugs for *gambiense* HAT in the near future, the top priority is improving the therapy of *rhodesiense* HAT. However, drug developers are confronted today with such low numbers of HAT cases that conducting clinical trials with sufficient statistical power becomes almost impossible.

Diagnosis: Improving the specificity of RDTs would transform the current complex diagnostic algorithm into a simple procedure, applicable at peripheral health facilities.

Asymptomatic carriers of *T. b. gambiense*: A fraction of CATT- or RDT-positive persons cannot be confirmed with parasitological techniques. Some of these are false positives but others are not, and they can act as a human reservoir if left untreated. Today only trypanolysis is able to confirm the presence of *gambiense*-specific antibodies as a surrogate for contact with the parasite¹³⁵⁻¹³⁷. In a context of *gambiense* HAT elimination, a high throughput alternative for TL with the same high specificity would greatly facilitate the identification of human trypanosome carriers.

Animal reservoir of *T. b. gambiense*: It is known that domestic and wild animals can be hosts of *T. b. gambiense*, and this may be the cause of HAT re-emergence in eliminated foci^{138,139}. Testing of animals, including tsetse, may become part of the toolbox for post-elimination monitoring to ensure sustained zero-transmission in controlled HAT foci. It is therefore crucial to develop sensitive and *T. b. gambiense*-specific tools for such purpose.

Tables

Table 1 Institutions keeping small stocks of anti-trypanosome drugs

Institution	Address
Liverpool University Hospital, Royal Liverpool & Broadgreen NHS Foundation Trust	Prescot Street, Liverpool L7 8XP, United Kingdom
University College London Hospital, NHS Foundation Trust	Mortimer Market Centre off Capper Street, London WC1E 6JB, United Kingdom
FMH Innere Medizin und Tropen- und Reisemedizin, Schweizerisches Tropen und Public Health Institut	Socinstrasse 57, CH 4002 Basel, Switzerland
Hôpitaux Universitaires de Genève, Service de Médecine Internationale et Humaine	Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland
Centers for Disease Control and Prevention	1600 Clifton Road, Mailstop D-09, Atlanta, GA 30333, USA
University of Tokyo, Institute of Medical Science, Division of Infectious Diseases	4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
Universitair Ziekenhuis Antwerpen	Wilrijkstraat, 10, 2650 Edegem, Belgium
Erasmus Medical Center	Dr Molewaterplein 40, Rotterdam 3015, The Netherlands
Netcare Milpark Hospital	9 Guild Road, Parktown West, Johannesburg 2193, South Africa

Table 2: Standard treatment for human African trypanosomiasis

HAT form and stage	First-line treatment	Dosage	Alternative treatment
<i>gambiense</i>			
First-stage	Pentamidine	4 mg/kg/day i.m. or i.v. (diluted in normal saline, in 2-h infusions) x 7 days	
Second-stage	Nifurtimox-eflornithine combination therapy (NECT)	Nifurtimox 15 mg/kg/day orally in three doses x 10 days Eflornithine 400 mg/kg/day i.v. in two 2-h infusions (each dose diluted in 250 ml water for injection) ^a x 7 days	Eflornithine 400 mg/kg/day i.v. in four 2-h infusions (each dose diluted in 100 ml water for injection) ^a x 14 days Third-line (e.g. treatment for relapse): Melarsoprol 2.2 mg/kg/day i.v. x 10 days
<i>rhodesiense</i>			
First-stage	Suramin	Test dose of 4–5 mg/kg i.v. (day 1), then 20 mg/kg i.v. weekly x 5 weeks (maximum 1 g /injection) (e.g. days 3, 10, 17, 24, 31)	Pentamidine 4 mg/kg/day i.m. or i.v. (diluted in normal saline, in 2-h infusions) x 7 days
Second-stage	Melarsoprol	2.2 mg/kg/day i.v. x 10 days	

i.m., intramuscularly; i.v., intravenously

^aChildren < 10 kg: dilute in 50 ml of water for injection. Children 10 to 25 kg: dilute in 100 ml of water for injection. If water for injection is unavailable, eflornithine can be diluted in 5% dextrose or normal saline.

Figures

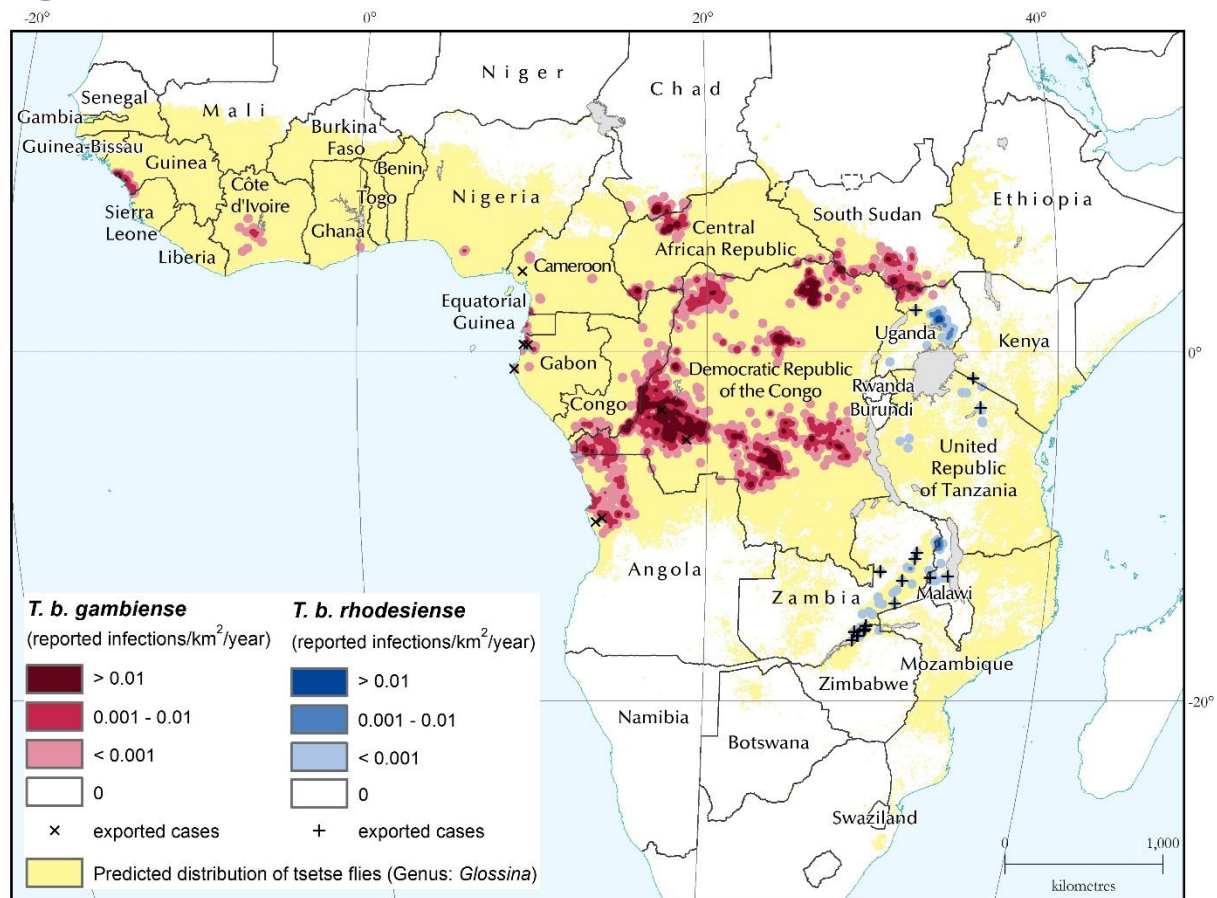


Figure 1: Geographic distribution of reported infections of Human African Trypanosomiasis (Reporting period: 2010-2014).

Gambiense HAT is found in Western and Central Africa, while *rhodesiense* HAT is found in Eastern and Southern Africa. The source of reported infections is the WHO Atlas of HAT ¹. The density of reported infections (i.e. the number of reported infections/km²/year) is obtained from the village-level data by kernel smoothing ¹², using a search radius of 30 km ¹¹⁹. 'Exported cases', i.e. those diagnosed in non-endemic countries, are mapped in the probable place of infection ³. The predicted distribution of tsetse flies is provided by the Programme against African Trypanosomiasis (<http://www.fao.org/ag/againfo/programmes/en/paat/home.html>).

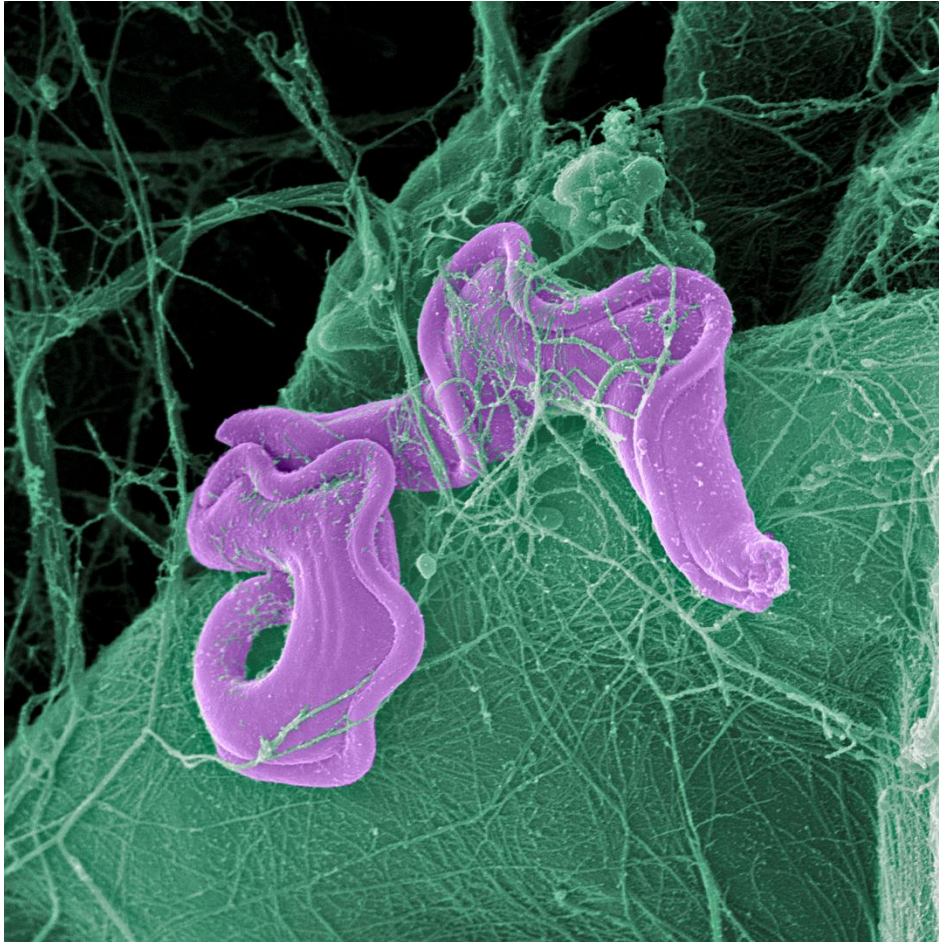


Figure 2: False-colored scanning electron microscopy image, 14 x 14 microns, showing trypanosomes (purple) and an adipocyte (green) in the ear dermis of a *Trypanosoma brucei* in infected mouse. **Credits:** David Pérez-Morga and Marjorie Vermeersch (Université Libre de Bruxelles), Guy Caljon (Antwerp University) and Jan Van den Abbeele (Institute of Tropical Medicine Antwerp)³⁶.

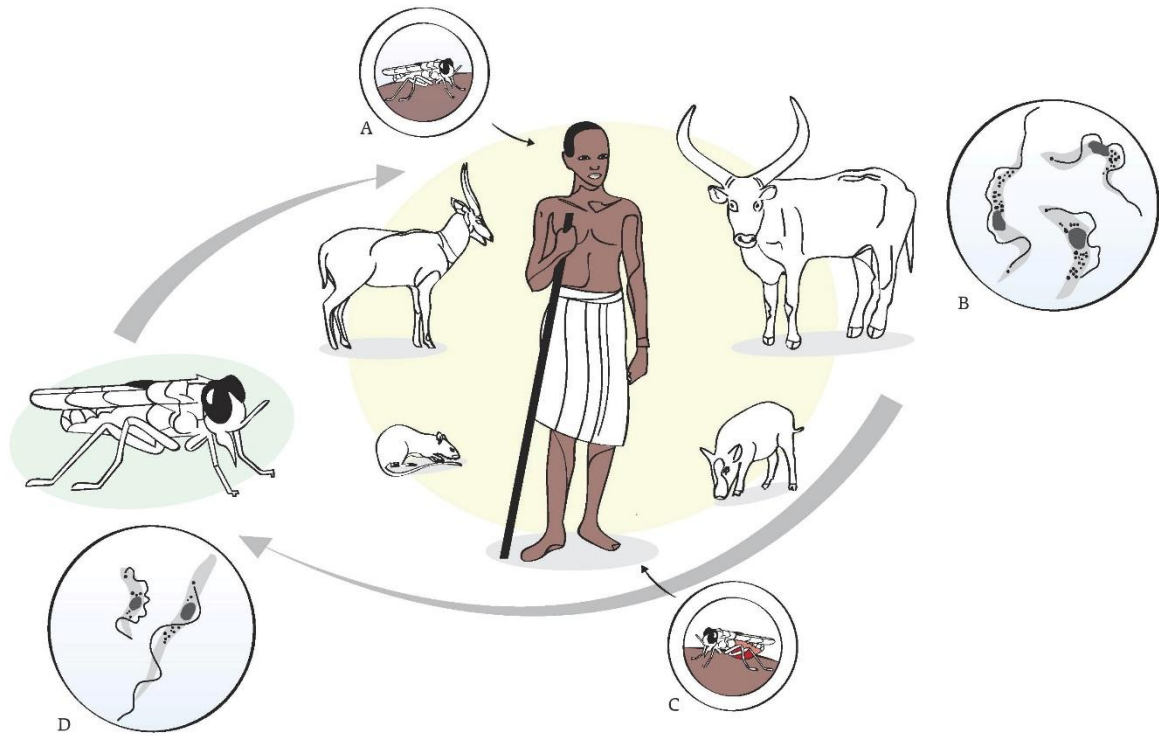


Figure 3: Life cycle of *Trypanosoma brucei*.

(A) Metacyclic trypanosomes are injected in the skin of a mammalian host, together with saliva containing anticoagulant factors. (B) Once in the mammalian host, trypanosomes transform into dividing long slender forms that, via lymph and blood, can infiltrate tissues and organs, including the brain parenchyma. Some transform into a non-dividing short stumpy form. (C) A tsetse fly is infected by taking blood from a human or other mammal that contains stumpy trypanosomes. (D) After about two weeks, trypanosomes may have colonised the salivary glands producing free swimming metacyclic trypanosomes, which can then be transmitted to the next mammalian host.

Source: © Food and Agriculture Organization of the United Nations. Reproduced with permission.

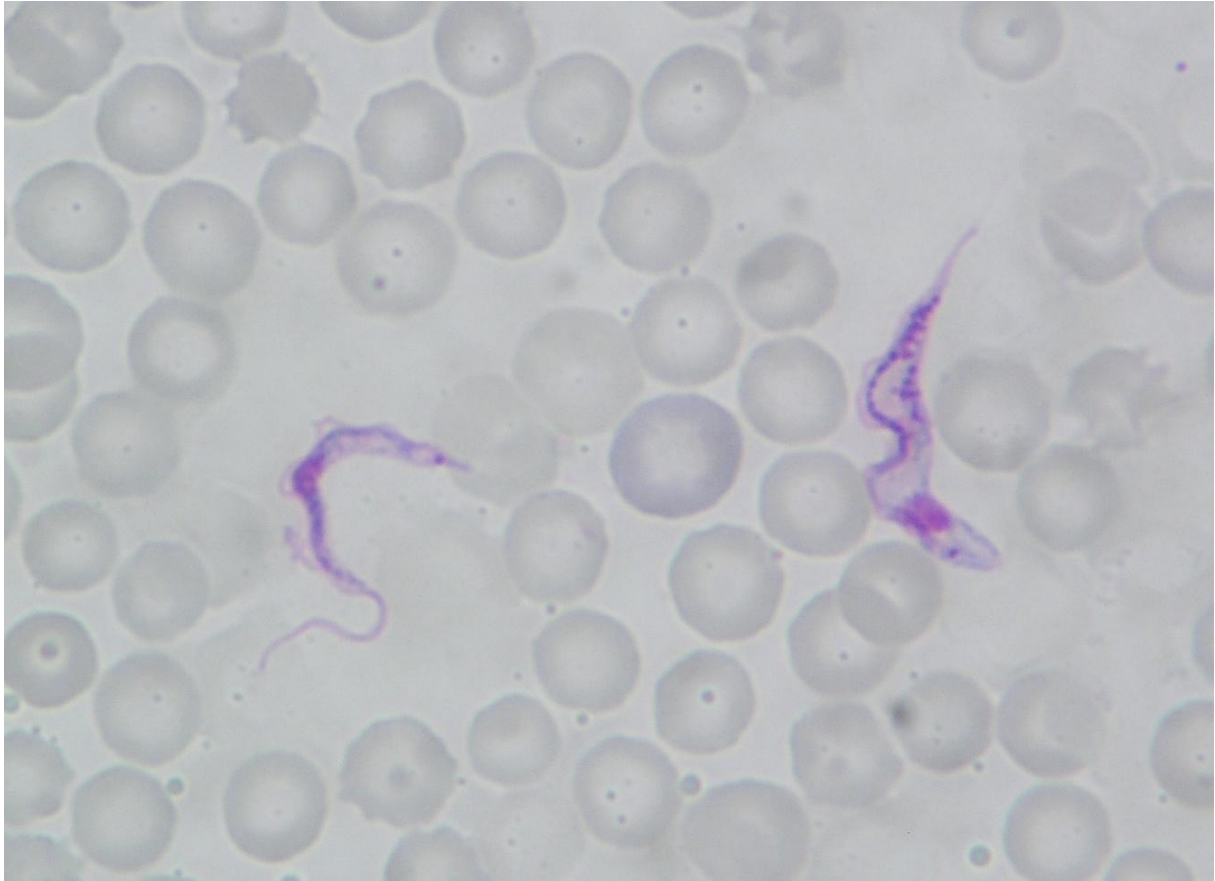


Figure 4: Giemsa stained thin blood film with one long-slender (right side) and one short stumpy trypanosome (left side).

FAST FACTS

Overview

Human African trypanosomiasis (HAT) is a so called "Neglected Tropical Disease" caused by infection with *Trypanosoma brucei*.

The disease caused devastating epidemics in the 20th century. Large scale control efforts brought the number of cases down to < 3000 in 2015. Still, HAT poses a heavy burden on the affected poor rural communities in Africa and intrinsically bears the risk of recrudescence when control measures are relaxed.

Since patients are also reported from non-endemic countries outside Africa, HAT should be considered in differential diagnosis for travellers, tourists, migrants and expatriates who visited or lived in endemic areas.

Epidemiology

Two morphologically identical parasites can cause HAT. *Trypanosoma brucei gambiense* accounts for >95% of all cases and is endemic in Western and Central Africa, particularly in the Democratic Republic of the Congo. *T. b. rhodesiense* occurs in Eastern and Southern Africa, with most patients reported in Uganda and Malawi. Both are transmitted by tsetse, hematophagous, daytime feeder flies unique to sub-Saharan Africa.

People contract the disease while farming, fishing, hunting, collecting water or wood or other activities that expose them to the bite of an infective tsetse, e.g. visiting a game park. All age groups and both sexes are at risk.

Clinical presentation and diagnosis

The disease evolves from the first, hemo-lymphatic stage towards the second, meningo-encephalitic stage when trypanosomes cross the blood-brain barrier and invade the central nervous system (CNS).

Rhodesiense HAT is typically acute, progressing to second-stage within a few weeks and to death within 6 months. *Gambiense* HAT follows a chronic progressive course, with a mean duration of 3 years. In non-native patients, the incubation period is shorter and the clinical picture is acute and febrile, regardless of the subspecies.

At the site of the tsetse bite, a chancre may appear within 2-3 days, more frequently in *rhodesiense* than in *gambiense* HAT, often with satellite lymphadenopathy.

Most common first stage symptoms are long-lasting intermittent fever, headache, pruritus and, in *gambiense* HAT, cervical lymphadenopathy.

In the second stage, neuropsychiatric disorders add to the first-stage features. The characteristic sleep disorder, which elicited the name *sleeping sickness*, consists of daytime somnolence plus sudden overwhelming sleep urges, and nocturnal insomnia. Other neurological signs comprise hyper- or hypo-tonicity, tremor of hands and fingers, choreiform, athetoid, or oscillatory movements, fasciculation, motor weakness, ataxia, akinesia, and speech disorders. Perioral and cheiro-oral reflexes are frequently seen. Mental changes are common, including emotional lability, attention deficit, indifference, apathy, aggressive behaviour, stereotypic behaviour, dissociative fugue, manic episodes, melancholia, confusion, and dementia. Neuropsychiatric disorders increase with disease progression.

Infiltration of endocrine organs (mainly thyroid and adrenals) and the hypothalamic-hypophysial axis lead to disruption of circadian rhythms of hormonal secretion including prolactin, renin, growth hormone, and cortisol, but generally do not require specific treatment. Cardiac alterations are common and develop at early stages of HAT, featuring electrocardiogram abnormalities including QT-interval prolongation, repolarisation changes, and low voltage, consistent with peri-myocarditis⁵¹. In *gambiense* HAT these alterations are generally mild, but in *rhodesiense* HAT earlier and more severe, even fatal, peri-myocarditis and congestive cardiac failure are observed.

The *rhodesiense* HAT clinical features differ from *gambiense* HAT in that a trypanosomal chancre is more frequent, fever presents in both disease stages and more frequently in children, enlarged lymph nodes tend to be submandibular, axillary and inguinal, and edema is more frequent. Thyroid dysfunction, adrenal insufficiency and hypogonadism are more common, and myocarditis is more severe. Liver involvement with hepatomegaly and jaundice are frequent but usually moderate, sometimes with ascites^{54, 54}.

Diagnosis

Clinical symptoms and signs, even in second stage disease, are not specific. Antibody detection for *gambiense* HAT has proven very helpful in control operations in endemic areas as well as in differential diagnosis but demonstration of the parasite in chancre exudate, lymph node aspirate, blood or cerebrospinal fluid is required to confirm the infection. Second stage disease is defined by abnormal cytorrachia (>5 cells/ μ l) or presence of trypanosomes in the cerebrospinal fluid. The most sensitive of the serological and parasitological tests are not widely available.

Treatment and prevention

Chemoprophylaxis and vaccination against HAT do not exist.

Treatment is generally effective, and it depends on the infecting agent and disease stage.

For *gambiense* HAT, first stage is treated with pentamidine and second stage with nifurtimox-eflornithine combination therapy. For *rhodesiense* HAT, first stage is treated with suramin and second stage with melarsoprol.

These drugs have different degrees of toxicity and can cause serious adverse effects, especially melarsoprol.

All drugs are donated by the manufacturers and can be obtained on request from the World Health Organization at no charge.