

Human African trypanosomiasis

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Human African trypanosomiasis (sleeping sickness) is a parasitic infection that almost invariably progresses to death unless treated. Human African trypanosomiasis caused devastating epidemics during the 20th century. Thanks to sustained and coordinated efforts over the past 15 years, the number of reported cases has fallen to an historically low level. Fewer than 3000 cases were reported in 2015, and the disease is targeted for elimination by WHO. Despite these recent successes, the disease is still endemic in parts of sub-Saharan Africa, where it is a considerable burden on rural communities, most notably in central Africa. Since patients are also reported from non-endemic countries, human African trypanosomiasis should be considered in differential diagnosis for 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 suboptimal, but ongoing clinical trials provide hope for safer and simpler treatments.

Introduction

Human African trypanosomiasis is a neglected tropical disease that occurs in sub-Saharan Africa, within the distributional limits of the vector, the tsetse fly. Two forms of the disease exist: the slow-progressing form, caused by *Trypanosoma brucei gambiense*, which is endemic in western and central Africa; and, the faster-progressing form, caused by *Trypanosoma brucei rhodesiense*, found in eastern and southern Africa.¹

Since the beginning of the 20th century, human African trypanosomiasis has killed millions of people. Today, the disease is rare, thanks to large-scale and efficient deployment of an—albeit incomplete—arsenal of control tools. Yet, cases are reported from more than 20 countries in Africa, where the disease causes substantial morbidity among the affected rural populations, and continues to pose the threat of severe epidemics.² In a globalised world, cases are also diagnosed outside endemic African countries among travellers, tourists, expatriates, and migrants.³ In this Seminar, we discuss the epidemiology, cause, clinical features, diagnosis, and treatment of human African trypanosomiasis, and touch on epidemiological surveillance and methods of control and elimination.

Epidemiology

The trypanosomes that cause human African trypanosomiasis are classically transmitted by the bite of blood-sucking tsetse flies (Diptera, genus *Glossina*). *T brucei gambiense* can also be transmitted congenitally.^{4,6} Other routes of transmission are possible but poorly documented, and are thought to be very rare (eg, sexual, laboratory accidents, blood transfusion, and organ transplantation).^{6,9}

In the early 20th century, devastating epidemics occurred in, among other places, Uganda, Congo Free State (now Democratic Republic of the Congo), Cameroon, and other western African countries, which were probably triggered by ecological disruptions and forced population movements brought about by colonialism.¹⁰ Since then, the intensity of control efforts and extent of *T brucei* transmission have been closely linked. In some endemic areas, changes in

land use and climate dramatically reduced tsetse populations and interrupted *T brucei* transmission.¹¹ Neglecting human African trypanosomiasis, either because of social or political instability or the tyranny of success, will inevitably lead to resurgence. The last alarming peak in transmission occurred in the late 1990s, and robust and coordinated efforts were required to bring about disease control.

In 2015, 2804 cases of human African trypanosomiasis were reported to WHO, of which 2733 were caused by *T brucei gambiense* (90% reduction since 1999) and 71 were caused by *T brucei rhodesiense* (89% reduction since 1999); this number includes cases diagnosed in both endemic and non-endemic countries. The bulk of the case load of *T brucei gambiense* disease continues to be in the Democratic Republic of the Congo (86% of cases), followed by the Central African Republic and Chad (5% and 2%, respectively). As of 2015, these countries were the only ones to report more than 50 cases per year. However, the probable under-detection of cases of human African trypanosomiasis should be taken into account when reported incidence is assessed. For example, in South Sudan, an area of civil unrest, and Guinea, an area of Ebola virus disease outbreak, the

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Search strategy and selection criteria

We searched PubMed on Dec 1, 2016, for publications written in English or French, using the keywords: “sleeping sickness”, “*Trypanosoma brucei gambiense*”, “*Trypanosoma brucei rhodesiense*”, “CATT”, “suramin”, “pentamidine”, “melarsoprol”, “eflornithine”, “tsetse”, “*Glossina*”, or “human African trypanosomiasis”. Results were limited to those published between 2010 and 2016. Among the almost 3000 references, we selected those we judged relevant, prioritising those reporting applied research. An additional source was the Programme Against African Trypanosomiasis Tsetse and Trypanosomiasis Information Bulletin (2010–2015), edited by the Food and Agriculture Organization of the United Nations. Additional references were retrieved from the personal databases of all coauthors.

reported and actual incidence of disease might differ considerably. The case load of *T brucei rhodesiense* disease is concentrated in Malawi and Uganda, which account for 82% of cases.¹²

Although animal African trypanosomiasis, or *nagana*, is widespread in all tsetse-infested areas, human African trypanosomiasis is characterised by a markedly focal distribution (figure 1). This patchy distribution is the result of complex interactions between parasite, vector, host, and the environment, which are not yet fully understood. The disease is usually found in rural areas with suitable habitats for the tsetse fly vector and frequent human-tsetse contact. Periurban areas can also be affected, especially where riverine tsetse species have adapted to anthropic environments.^{17–19} 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 (eg, the predominantly male activities of hunting and fishing, or the predominantly female activities of water fetching and small-crop growing).

Human beings are thought to be the main reservoir of *T brucei gambiense*, and domestic and wild animals the main reservoirs of *T brucei rhodesiense*. Although domestic and wild animals can also host *T brucei gambiense*, their epidemiological role remains unclear.²⁰ For people, *T brucei rhodesiense* infection leads to death within 6 months.

Exported cases of human African trypanosomiasis are reported from all continents,³ with most cases being *T brucei rhodesiense* disease in tourists who have visited national parks and game reserves in Tanzania, but also in Kenya, Malawi, Uganda, Zambia, and Zimbabwe. Exported cases of *T brucei gambiense* disease are rarer, and include migrants, refugees, and long-term expatriates. Exceptionally long periods (up to 30 years, and possibly more) can separate infection and diagnosis;^{21,22} thus, *T brucei gambiense* disease 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 family of exclusively parasitic organisms found in vertebrates and

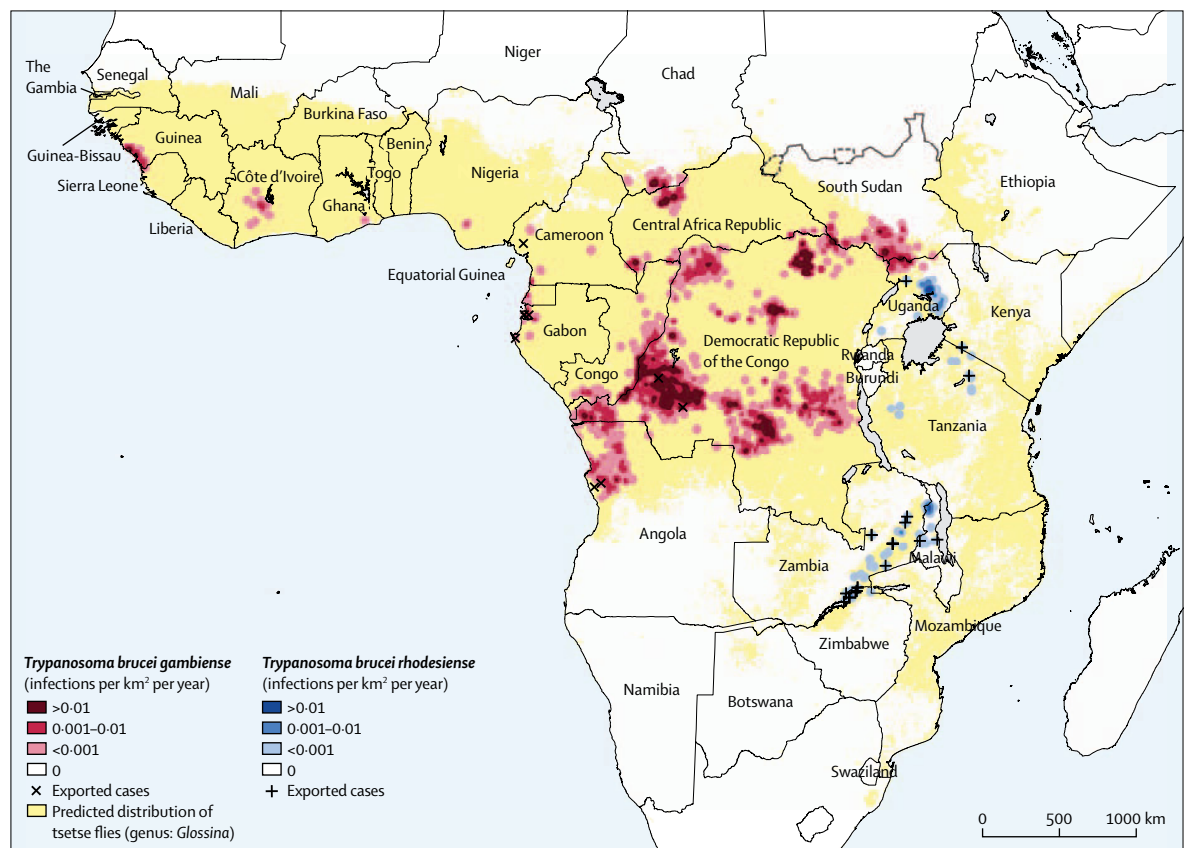


Figure 1: Geographical distribution of reported infections of human African trypanosomiasis (reporting period 2010–14)

Trypanosoma brucei gambiense disease is found in western and central Africa, whereas *Trypanosoma brucei rhodesiense* disease is found in eastern and southern Africa. The source of reported infections is the WHO Atlas of human African trypanosomiasis.^{1,3} The density of reported infections (ie, the number of reported infections per km² per year) was obtained from village-level data by kernel smoothing,¹⁴ with a search radius of 30 km.¹⁵ Exported cases (ie, those diagnosed in non-endemic countries) are mapped in the probable place of infection.³ The predicted distribution of tsetse flies was provided by the Programme against African Trypanosomiasis.¹⁶

insects worldwide.²³ These unicellular parasites have co-evolved with their hosts to such an extent that most are commensal rather than pathogenic.²⁴ *T brucei* includes three morphologically indistinguishable subspecies (figure 2): *T brucei brucei*, which causes animal African trypanosomiasis, and is not infective to human beings, whereas *T brucei rhodesiense* and *T brucei gambiense* can infect people because they are resistant to apolipoprotein A1 (a serum protein that triggers death in other trypanosomes).^{26,27} All *T brucei* cells contain a nucleus, a mitochondrion that contains the kinetoplast, and a flagellum attached to the cell by an undulating membrane. During its lifecycle (figure 3), which alternates between a mammalian and an insect (tsetse fly) host, *T brucei* remains extracellular and undergoes important metabolic adaptations that are reflected by morphological changes.

In the blood and tissues of mammals, trypanosomes are most often observed as spindle-shaped cells that are 20–30 μm long (about three times the diameter of a human erythrocyte) and 2–5 μm wide, and are characterised by their wriggling movement. Sometimes, shorter forms are observed: these are metabolically preadapted to survive in the tsetse intestines (figure 4). In the mammalian host, the trypanosome cell membrane is covered by a dense coat of identical glycoprotein dimers that shields the underlying membrane against innate immunological attacks, such as by complement. These highly immunogenic glycoproteins induce a specific antibody response that triggers the destruction of all antibody-opsonised trypanosomes. To survive this antibody-mediated immune response, trypanosomes developed antigenic variation, whereby the glycoprotein coat is replaced by an antigenically different coat. Between 1×10^3 and 1×10^6 coat switches are estimated to occur per population doubling within the mammalian host.^{28,29} The interplay between the immune response of the host and antigenic variation of the parasite results in irregular fluctuations in parasitaemia, reflected by intermittent fevers accompanying destruction of trypanosomes. *T brucei* infection usually induces polyclonal B-cell activation, resulting in extremely high IgM concentrations (up to 14 times normal values) and various non-trypanosome-specific antibodies, including autoantibodies. These antibodies, both specific and non-specific, take part in the pathogenesis of the infection and cause non-specific reactions in antibody detection tests for other infections.^{30–32} 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 various peripheral organs and tissues. The parasites then invade the brain parenchyma, where they trigger local inflammation and neurological damage.³³ The parasite's journey through the mammalian host is both



Figure 2: False-coloured scanning electron microscopy image, 14 $\mu\text{m} \times 14 \mu\text{m}$, showing trypanosomes (purple) and an adipocyte (green) in the ear dermis of a *Trypanosoma brucei*-infected mouse. Adapted with permission from David Pérez-Morga and Marjorie Vermeersch (Université Libre de Bruxelles, Gosselies, Belgium), Guy Caljon (Antwerp University, Antwerp, Belgium), and Jan Van den Abbeele (Institute of Tropical Medicine, Antwerp, Belgium).²⁵

accompanied and regulated by complex and diverse immunological reactions, some of which are pathogenic and induced by components of the parasite and tsetse fly saliva.³⁴

T brucei depends on tsetse flies for its cyclical transmission (video 1). Both sexes are haematophagous (blood-feeding) and can transmit trypanosomes. Tsetse flies 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. The 31 tsetse species and subspecies are classified as forest, riverine, or savannah, according to morphological differences and habitat preference.³⁵ *Glossina fuscipes* and *Glossina palpalis* (from the palpalis riverine group) are the main vectors of *T brucei gambiense*.^{36,37} For *T brucei rhodesiense*, the main vectors are *G f fuscipes* (in Uganda) and the savannah-group species, which include *Glossina morsitans* and *Glossina pallidipes*.^{38,39} Tsetse flies are infected with *T brucei* when they ingest trypanosomes in the blood or, as shown in experimental infections, in the skin of mammals.^{25,40} 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 forms, which are free-swimming and resemble the short stumpy form in shape.⁴¹ In a natural population of tsetse flies, only a small proportion (about 0.01%) carry a mature infection of *T brucei* (ie, with metacyclic trypanosomes in the salivary glands^{42,43}), but a tsetse fly, feeding every 3 days, can infect several people during its 2–3-month lifespan. Eliminating the tsetse or reducing contact between tsetse and human beings is one way to reduce or interrupt transmission of *T brucei*.

See Online for video 1

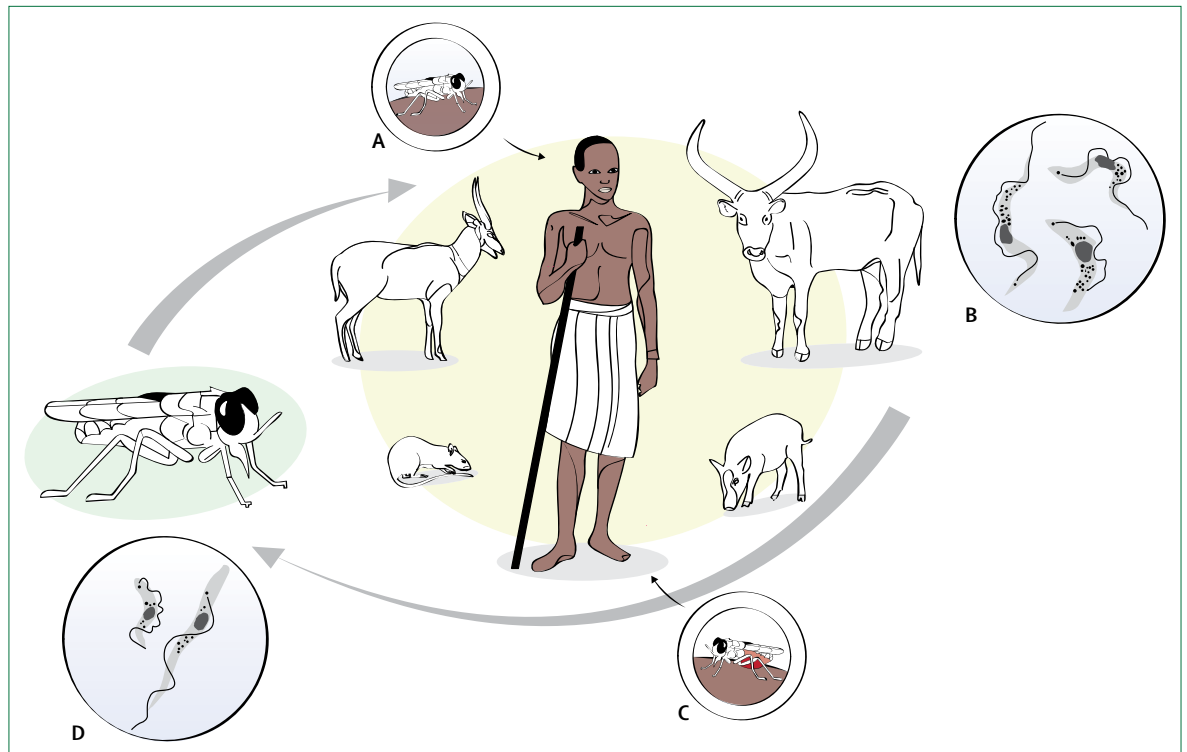


Figure 3: Lifecycle of *Trypanosoma brucei*

(A) Metacyclic trypanosomes are injected into 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 being or other mammal that contains stumpy trypanosomes. (D) After about 2 weeks, trypanosomes might have colonised the salivary glands, producing free-swimming metacyclic trypanosomes that can then be transmitted to the next mammalian host. Source: © Food and Agriculture Organization of the United Nations. Reproduced with permission.

Clinical features

The clinical presentation of human African trypanosomiasis depends on the *T brucei* subspecies, host response, and disease stage. Variations of virulence and pathogenicity are attributed to different strains of parasite.^{44,45} Generally, both forms of the disease lead to death if untreated; although, for *T brucei gambiense* disease, healthy carriers and self-cure have been described.⁴⁶ *T brucei rhodesiense* disease is typically acute, progressing to second-stage disease within a few weeks, and death within 6 months.^{47,48} *T brucei gambiense* disease follows a chronic progressive course, with a mean duration estimated at 3 years, albeit with high interpersonal variability.⁴⁹

The disease goes through two stages: a haemolympathic stage followed by a meningoencephalitic stage in which trypanosomes cross the blood–brain barrier and invade the CNS. Neurological disturbances, including sleep disorder, are typical of second-stage disease; however, most signs and symptoms are common to both stages.

A 3–4-cm dermal reaction at the site of the tsetse bite (inoculation chancre) appears within 2–3 days in 5–26% of Bantu people who contract *T brucei rhodesiense*; in people from other regions, this reaction occurs more frequently. This reaction is rarely seen in those with *T brucei gambiense* disease.^{44,50}

First-stage *T brucei gambiense* disease presents predominantly with intermittent fever lasting 1 day to 1 week, separated by intervals of days or months, as well as headache, pruritus, and lymphadenopathy (mainly posterior cervical but also possible in the axillar, inguinal, and epitrochlear regions). Hepatosplenomegaly, oedema, and endocrine dysfunction (amenorrhoea, infertility, and miscarriage in women; reduced libido and impotence in men) present less frequently.

In second-stage disease, neuropsychiatric disorders accompany first-stage features, and fever becomes less frequent. The characteristic sleep disorder, from which the name sleeping sickness is derived, consists of daytime somnolence and sudden overwhelming sleep urges, and nocturnal insomnia. Polysomnographic records show a disruption of the sleep–wake cycle with frequent, short, sleep-onset rapid eye movement episodes that are equally likely to occur during day and night.^{51–53}

Other neurological signs include: hypertonicity or hypotonicity; tremor of the hands and fingers; 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 and include emotional lability, attention deficit, indifference,

apathy, aggressive behaviour, stereotypic behaviour, dissociative fugue, manic episodes, melancholia, confusion, and dementia. Neuropsychiatric symptoms increase in frequency and severity with disease progression.⁵⁴ Trypanosome 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 cortisol⁵¹ but generally do not require specific treatment. Cardiac alterations are common but do not have the same clinical relevance as in Chagas disease (American trypanosomiasis). Cardiac alterations develop early, with electrocardiogram abnormalities consistent with perimyocarditis (QT-interval prolongation, repolarisation changes, and low voltage) being most common.⁵⁵ In *T brucei gambiense* disease, these alterations are generally mild; in *T brucei rhodesiense* disease, earlier and more severe perimyocarditis and congestive cardiac failure are reported.⁵⁶

The clinical features of *T brucei rhodesiense* disease are similar to those of *T brucei gambiense* disease, but trypanosomal chancre occurs more frequently, often with satellite lymphadenopathy. Fever presents in both disease stages, and more frequently in children than adults.⁵⁷ Enlarged lymph nodes tend to be submandibular, axillary, and inguinal in *T brucei rhodesiense* disease, rather than posterior cervical as in *T brucei gambiense* disease; additionally, oedema is reported more frequently in the former than the latter. Thyroid dysfunction, adrenal insufficiency, and hypogonadism are more common than in *T brucei gambiense* human African trypanosomiasis, and myocarditis is more severe and can be fatal. Liver involvement with hepatomegaly and jaundice are frequent but usually moderate, sometimes with ascitis, and generally occur less frequently in *T brucei gambiense* disease.⁵⁸ In southeastern African countries, in particular Malawi, a more chronic form has been reported: it has a longer first stage, with fewer neurological disorders and an absence of chancre.⁴⁴ Compared with locals, in travellers from non-endemic countries the incubation period is shorter (<3 weeks for *T brucei rhodesiense* human African trypanosomiasis and <1 month for *T brucei gambiense* human African trypanosomiasis) and the clinical picture is acute and febrile from the onset, regardless of the subspecies. A trypanosomal chancre is reported more frequently (88% in *T brucei rhodesiense* disease and 56% in *T brucei gambiense* disease) and a rash, consisting of non-itching, irregular erythematous macules of up to 10 cm in diameter often with a central area of normally coloured skin, develops in a third of cases.⁵⁹ The rash might last several weeks, vanishing and reappearing in different areas.⁶⁰ Headache, lymphadenopathy, hepatomegaly, and splenomegaly occur in a quarter to half of patients. In travellers with *T brucei rhodesiense* disease, gastrointestinal symptoms are more frequent, with jaundice reported in

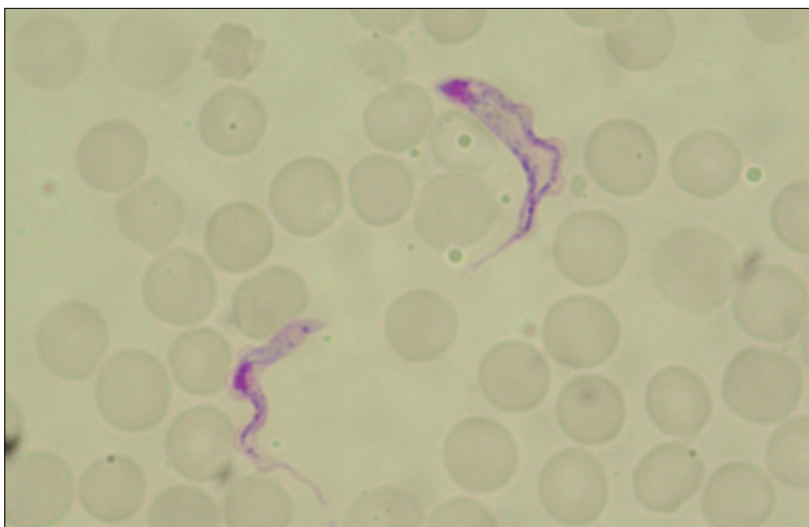


Figure 4: Giemsa-stained thin blood film with one long slender (left side) and one short stumpy trypanosome (right side)

28% of cases. Less frequent but severe complications include renal failure requiring haemodialysis, multi-organ failure, disseminated intravascular coagulopathy, and coma.^{3,61}

Diagnosis

Clinical signs and symptoms of human African trypanosomiasis are unspecific and can easily be mistaken for those of other diseases; thus, they are often insufficient for diagnosis.

Reliable serodiagnostic tests exist only for *T brucei gambiense* infection, and are based on the detection of specific antibodies. The card agglutination test for trypanosomiasis (CATT),⁶² developed almost 40 years ago, has been pivotal in the control of *T brucei gambiense* disease. CATT can be done with blood collected from a finger prick, plasma, or serum, and the agglutination reaction is scored visually after 5 min. It is particularly suited for screening of at-risk populations by mobile teams.⁶³

Recently, rapid diagnostic tests for *T brucei gambiense* infection were developed and introduced: the HAT Sero-K-SeT (Coris BioConcept, Gembloux, Belgium) and the SD Bioline HAT 1.0 (Standard Diagnostics, Yongin, South Korea).^{64–66} The major advantage, over CATT, is that these tests fully comply with the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria;⁶⁷ therefore, they are more suitable for passive screening and surveillance in fixed health centres in endemic countries that often lack electricity and laboratory infrastructure.⁶⁸ Second-generation cassette and strip-format rapid diagnostic tests, including recombinant antigens, are under development.^{69–71}

Although useful for screening of at-risk populations and identification of individuals as probably infected

with *T brucei gambiense*, CATT and rapid diagnostic tests are not 100% specific.⁷² Particularly when disease prevalence is low, their positive predictive value becomes critically low⁷³—eg, with a specificity of 98% and a prevalence of 0·1%, the positive predictive value is 4·5%. Currently, in most human African trypanosomiasis foci, prevalence is far below 0·1% and serological screening tests yield about 99 false-positive results for every true positive.

Immune trypanolysis and ELISAs are applicable in laboratory conditions on serum, plasma, and dried blood spots.^{31,72,74,75} Their high specificity and sensitivity, their applicability to dried blood spots, and adaptability to animal specimens make them excellent tools for large-scale surveys, post-elimination monitoring, and animal reservoir studies.^{76,77}

No field-applicable serodiagnostic test exists for *T brucei rhodesiense* infection. Efforts to develop second-generation rapid diagnostic tests able to detect both *T brucei gambiense* and *T brucei rhodesiense* infection are ongoing, but the risk of cross-reaction with antibodies against non-human infective trypanosomes is ever-present.^{68,69} Because cases of *T brucei rhodesiense* disease usually present with high levels of parasitaemia, antibody detection is less relevant.³⁶ Parasitological confirmation of *T brucei gambiense* infection is achieved by microscopic examination of a lymph node aspirate (video 2) or by concentration techniques applied on blood (mini-anion exchange centrifugation technique or microhaematocrit centrifugation technique) (video 3) or on cerebrospinal fluid (modified single centrifugation technique).^{77–82} Importantly, to detect the colourless, motile trypanosome at low magnification (10×10, 16×10, or 10×40), the microscope should be adjusted for maximum light diffraction. The diagnostic sensitivity of these techniques is suboptimal (maximum 90%) although the analytical sensitivity of, for example, the mini-anion exchange centrifugation technique is less than 50 trypanosomes per mL of blood.⁸³ For *T brucei rhodesiense* infection, which usually presents 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 (ie, assessment of neurological involvement) relies on the examination of cerebrospinal fluid collected by lumbar puncture.⁸⁴ Patients with five or fewer white blood cells per μL and no trypanosomes in the cerebrospinal fluid are classified as first stage, and those with more than five white blood cells per μL or trypanosomes in the cerebrospinal fluid as second stage.³⁶ Other markers for neuroinflammation (eg, intrathecal IgM and neopterin) have been proposed for improved stage determination; however, the added value of IgM is minimal and the quantification of neopterin is not currently possible under field conditions.^{85,86}

Molecular diagnosis of human African trypanosomiasis, 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 cases.⁸⁷ All formats have poor diagnostic accuracy (even for stage determination and post-treatment follow-up), poor reproducibility, and incompatibility with diagnostic facilities in endemic countries.^{88–90} In some instances, most notably in the context of disease elimination, identification of the subspecies of *T brucei* (eg, in tsetse, animals, and human beings) might be useful since atypical infections with animal trypanosomes are possible.^{37,91–97} *T brucei gambiense*-specific and *T brucei rhodesiense*-specific PCR assays exist, but they target single-copy genes; hence, their analytical sensitivity is poor.^{98,99}

Because diagnosis of human African trypanosomiasis is a specialty and techniques are not common, technical assistance and reference testing can be sought from the two WHO Collaborating Centres for human African trypanosomiasis (ie, the Institute of Tropical Medicine in Antwerp, Belgium, and the Institut de Recherche pour le Développement, based at the Centre International de Recherche et Développement sur l'Élevage en zones Subhumides, in Bobo Dioulasso, Burkina Faso).¹⁰⁰

Treatment

Five drugs are routinely used in the treatment of human African trypanosomiasis: pentamidine and suramin to treat first-stage disease, and melarsoprol, eflornithine, and nifurtimox for second-stage disease. All are donated by the manufacturers, and WHO ensures their worldwide distribution free of charge. The drugs can be obtained directly from WHO in Geneva or from the few institutes that stock them (appendix).³ This accessibility means treatment of human African trypanosomiasis is unaffected by counterfeit and substandard drugs.

The earlier human African trypanosomiasis is treated, the better the prospects of treatment tolerability and cure. The choice of treatment depends on the causative agent and disease stage (table). Drugs for the treatment of first-stage disease will generally not cure second-stage disease. Similarly, the use of second-stage drugs is not justified in the treatment of first-stage disease because the second stage requires drugs that cross the blood–brain barrier, and such drugs tend to be more toxic and complex to administer than first-stage drugs.

First-stage treatment

Pentamidine isethionate is the first-line treatment for first-stage *T brucei gambiense* disease, and is an alternative treatment for *T brucei rhodesiense* disease; however, data on its efficacy in the latter role are limited.^{59,101} The efficacy of pentamidine against *T brucei gambiense* disease (95–98%) has been stable for decades: it is given intramuscularly once daily for 7 days but can also be given as an intravenous infusion in saline over 2 h. In endemic countries, pentamidine is more commonly delivered via intramuscular injection. Administration

See Online for video 2

See Online for video 3

See Online for appendix

should be preceded by the ingestion of sugar (10–20 g) to prevent hypoglycaemia, and followed by rest in the supine position for 1–2 h 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 problems.¹⁰²

Another treatment, suramin, is effective in the first stage of *T brucei gambiense* disease and *T brucei rhodesiense* disease, but is used only in the treatment of *T brucei rhodesiense* disease because of the risk of onchocerciasis co-infection in *T brucei gambiense*-endemic areas (ie, risk of allergic reactions arising from rapid killing of microfilaria), and because pentamidine administration is simpler. Suramin is administered as a slow intravenous infusion. It deteriorates rapidly in air and should be injected immediately after dilution. Recommended treatment schedules are complex and last up to 1 month. A test dose is administered before treatment because of the risk of acute hypersensitivity reactions. Adverse effects are frequent but mostly mild and reversible, and include pyrexia, nephrotoxicity, peripheral neuropathy, agranulocytosis, and thrombocytopenia.

Second-stage treatment

The first-line treatment for second-stage *T brucei gambiense* disease is nifurtimox–eflornithine combination therapy (NECT). In 2009, NECT was included in the WHO Essential Medicines List. Compared with melarsoprol or eflornithine monotherapy, NECT has higher cure rates (95–98%), lower fatality rates (<1%), less severe adverse events, simpler administration, and is believed to avoid causing drug resistance of the parasite.^{103–106} Nifurtimox is not licensed for African trypanosomiasis (only for American trypanosomiasis); thus, it can only be used to treat patients with African trypanosomiasis off label, subject to express authorisation and acceptance of responsibility by national authorities. WHO supplies endemic countries, free of charge, with a full NECT kit containing all drugs and materials needed for administration. NECT consists of nifurtimox delivered orally and eflornithine delivered intravenously. A dose of nifurtimox should be readministered if vomiting occurs within 30 min. With 14 infusions, instead of the 56 used in eflornithine monotherapy, NECT is easier to administer, demanding fewer hospital resources and reducing costs. Although the short half-life of eflornithine theoretically requires four daily infusions for a constant trypanostatic effect, infusions every 12 h are highly effective when combined with oral nifurtimox. The most common treatment-emergent adverse events are abdominal pain, vomiting, and headache.^{103,104,106–109} The toxicity profile replicates that of nifurtimox and eflornithine monotherapies, but with lower frequency and severity, most likely because of the shorter drug exposure. NECT is better tolerated in

	First-line treatment	Dosage	Alternative treatment and dosage
<i>Trypanosoma brucei gambiense</i>			
First stage	Pentamidine	4 mg/kg per day intramuscularly or intravenously (diluted in saline, in 2-h infusions) × 7 days	..
Second stage	Nifurtimox–eflornithine combination therapy	Nifurtimox 15 mg/kg per day orally in three doses × 10 days; eflornithine 400 mg/kg per day intravenously in two 2-h infusions (each dose diluted in 250 mL of water for injection)* × 7 days	Eflornithine 400 mg/kg per day intravenously in four 2-h infusions (each dose diluted in 100 mL of water for injection)* × 14 days; third-line (eg, treatment for relapse) is melarsoprol 2.2 mg/kg per day intravenously × 10 days
<i>Trypanosoma brucei rhodesiense</i>			
First stage	Suramin	Test dose of 4–5 mg/kg intravenously (day 1), then 20 mg/kg intravenously once per week × 5 weeks (maximum 1 g/injection—eg, days 3, 10, 17, 24, and 31)	Pentamidine 4 mg/kg per day intramuscular or intravenously (diluted in normal saline, in 2-h infusions) × 7 days
Second stage	Melarsoprol	2.2 mg/kg per day intravenously × 10 days	..

*Children weighing <10 kg: dilute in 50 mL of water for injection. Children weighing 10–25 kg: dilute in 100 mL of water for injection. If water for injection is unavailable, eflornithine can be diluted in 5% dextrose or saline.

Table: Standard treatment for human African trypanosomiasis by form and stage

children than in adults, and is generally better tolerated than eflornithine and melarsoprol monotherapies.

Eflornithine (α -difluoromethylornithine or DFMO) is given as a monotherapy for *T brucei gambiense* disease when the companion drug nifurtimox is unavailable or contraindicated. It is a cytostatic (ie, affects the host's cells) and trypanostatic (ie, affects trypanosome metabolism) drug. An active immune system is required to achieve cure: in patients who are immunocompromised, complete parasite elimination might not be achieved with eflornithine alone.¹¹⁰ Eflornithine as monotherapy is given as 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 in children and adults,¹¹¹ and a higher dose (600 mg/kg per day vs 400 mg/kg per day) in children younger than 12 years did not improve effectiveness.¹¹² Higher doses were not tested in adults. Eflornithine monotherapy has proved effective against *T brucei gambiense* disease (90–95% cure rate) but is not recommended for *T brucei rhodesiense* disease.^{103,113,114} Adverse events are frequent and similar to those of other cytostatics (including diarrhoea and neutropenia) but eflornithine is, on the whole, safer than melarsoprol, with fatality rates below 2%.¹¹³ The main adverse events are fever, pruritus, hypertension, nausea, vomiting, diarrhoea, abdominal pain, headaches, myelosuppression (anaemia, leucopenia, thrombocytopenia), and, more rarely, seizures that are generally isolated and respond to treatment.

Another treatment option is melarsoprol, but owing to the high frequency of severe and life-threatening adverse

drug reactions, and the availability of better alternatives, melarsoprol is restricted to the treatment of second-stage *T brucei rhodesiense* disease. In *T brucei gambiense* disease, 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 patients.¹¹⁵ Both the incidence and fatality rates of melarsoprol are higher in people with *T brucei rhodesiense* disease than those with *T brucei gambiense* disease,¹¹⁶ with fatality rates of approximately 9%¹¹⁷ and 6%,¹¹⁸ respectively. Coadministration of prednisolone might have a protective effect against the immune reaction thought to be a component of the encephalopathic syndrome. The encephalopathic syndrome usually occurs between 7 and 14 days after the first injection and is characterised by fever and convulsions, rapid onset of neurological disorders, progressive coma, or abnormal behaviour.¹¹⁹ Close monitoring of patients might allow detection of early signs, such as fever or headache, or both, leading to the cessation of melarsoprol and management with dexamethasone and diazepam.¹²⁰ Other frequent adverse reactions include pyrexia, headache, general malaise, gastrointestinal (nausea, vomiting, and diarrhoea), and skin reactions (pruritus); severe complications, such as exfoliative dermatitis, occur in less than 1% of cases.¹¹⁹ Cardiac failure is common and can be fatal, but might be attributable to human African trypanosomiasis itself.¹²¹

Drug resistance

Mutations in the genome of *T brucei gambiense* that confer 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 human African trypanosomiasis foci.^{122,123} The concern was alleviated with the introduction of NECT, which combines two drugs of different pharmacodynamics and modes of action, strongly decreasing the probability of resistance emergence.

Treatment in pregnancy

Although poorly studied, field experience has accumulated on the management of patients who are pregnant or lactating.³⁶ Pentamidine can be given after the first trimester of pregnancy. Nifurtimox, eflornithine, and melarsoprol, all of which are theoretically contraindicated, in practice are given when the mother is in advanced second-stage disease and her condition does not permit waiting. If postponement of treatment until childbirth is judged possible, a full course of pentamidine should be administered, principally to prevent vertical transmission. The benefits and risks should be clearly explained to the patient and her relatives. In *T brucei rhodesiense* disease, the acute clinical evolution usually precludes waiting until delivery, and suramin (also

theoretically contraindicated) or melarsoprol are given. Newborn babies should be examined clinically, and their blood checked for trypanosomes. Breastfeeding should continue during treatment.

Post-therapeutic follow-up

The assessment of treatment outcome requires following up the patient for up to 24 months with laboratory examinations of body fluids, including cerebrospinal fluid, because parasites can remain viable for long periods and cause relapses. In rural Africa, such a follow-up plan is challenging and cannot be performed systematically; instead, patients are advised to consult their doctor if symptoms reappear.

New drugs in the pipeline

Two new molecules in clinical development could revolutionise human African trypanosomiasis treatment. These molecules are administered orally and are intended for treatment of both disease stages; thus, the need for stage determination is eliminated. Fexinidazole, a nitroimidazole taken orally once a day for 10 days, is in phase 2/3 clinical trials near conclusion,¹²⁴ and a benzoxaborole, called SCYX-7158, taken in a single oral dose has entered phase 2/3 clinical trials.¹²⁵

Epidemiological surveillance

Surveillance is crucial for control of human African trypanosomiasis because of the disease's focal distribution, occurrence in remote rural areas, and capacity to re-emerge when control activities are relaxed. Control operations are resource-intensive and therefore require careful targeting. Surveillance is carried out by national control programmes, with support from WHO and other partners. Field data are collected through both active and passive case detection, and are assembled, harmonised, and geo-referenced at the village level in the Atlas of human African trypanosomiasis.^{2,126,127} The atlas provides maps of disease occurrence, risk levels, control activities, exported cases, and health facilities with capacity for diagnosis and treatment.^{1,3,5,128} Such maps provide crucial evidence to support the planning of control activities at national and subnational levels, and to monitor progress towards disease elimination.¹²⁹

Importantly, human African trypanosomiasis 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, human African trypanosomiasis is controlled through case detection and treatment, and, to a lesser extent, vector control.

For *T brucei gambiense* human African trypanosomiasis, the most effective control strategy is case finding and

treatment, which reduces the human reservoir and thus decreases *T brucei* transmission. Cases of *T brucei gambiense* disease are detected through active screening campaigns by mobile teams, consisting of up to eight people travelling in four-wheel drive vehicles or boats, and through passive screening in fixed health structures.¹²⁸ Diagnosis and treatment are resource-intensive activities 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 in risk of human African trypanosomiasis, this labour-intensive strategy is no longer cost-effective in the numerous low-prevalence settings. Moreover, where the disease is no longer perceived as a threat, populations are reluctant to participate in repeated, time-consuming screening activities.^{77,130,131} In low-prevalence settings, targeted door-to-door surveys focused on the immediate vicinities of former patients with human African trypanosomiasis may provide an alternative to mass screening, and complement passive case detection.¹³² Active screening can also be performed by so-called light mobile teams, consisting of one or two people travelling on motorbikes, who can reach villages or camps that are inaccessible to four-wheel drive vehicles.¹³³

In the current elimination context, it is also crucial to reinforce passive surveillance, integrating it into the general health-care system and focusing on self-presenting patients.^{134,135} Because passive surveillance relies on clinical suspicion followed by serological tests, it mostly detects patients with second-stage disease, who are likely to have fed the transmission cycle for years before detection.¹³⁶ It is therefore necessary to carry out reactive screening campaigns in the probable areas of infection of these patients.

Although vector control in *T brucei gambiense* disease settings has been limited by the availability of better options, improved tools and strategies, such as low-cost small insecticide-treated screens (so-called tiny targets), have enhanced traditional disease control in some epidemiological settings.¹³⁷ Other tsetse control tools, such as insecticide-treated cattle, also exist and can be cost effective in the appropriate settings and in a One Health framework.^{138,139} To date, insecticide resistance has not been reported in tsetse. For *T brucei rhodesiense* disease, control of the domestic animal reservoir is key. Blanket treatment of cattle, the reservoir, and amplifier closest to human beings, and insecticide application on these animals, have been used to contain epidemics.^{140,141} Other methods include targeted bush clearing, aerial or ground spraying of insecticide, insecticide-impregnated nets and screens, fly traps, and release of sterile male tsetse. Integration of several methods in a combined approach is recommended.¹⁴² By contrast, controlling the wild animal reservoir is far more challenging.

Travellers to endemic areas can take measures to prevent tsetse bites—eg, avoiding specific places known

Panel: Research priorities

Treatment

Although there is hope that two safe drugs for the treatment of human African trypanosomiasis caused by *Trypanosoma brucei gambiense* will be available in the near future, the top research priority is improving therapies for disease caused by *Trypanosoma brucei rhodesiense*. Drug developers are confronted with such low numbers of cases that conducting clinical trials with sufficient statistical power is almost impossible.

Diagnosis

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

Asymptomatic carriers of *T brucei gambiense*

A fraction of people who are positive for *T brucei gambiense* following card agglutination test or rapid diagnostic tests cannot have the diagnosis confirmed with parasitological techniques. Some are false positives but others are not, and the latter can act as a human reservoir if left untreated. Nowadays, only trypanolysis can confirm the presence of *T brucei gambiense*-specific antibodies as a surrogate for contact with the parasite.¹⁴³⁻¹⁴⁵

To eliminate *T brucei gambiense* disease, a high throughput alternative with the same specificity as trypanolysis would greatly facilitate the identification of human trypanosome carriers.

Animal reservoir of *T brucei gambiense*

Domestic and wild animals can be hosts of *T brucei gambiense*, and this reservoir might be the cause of human African trypanosomiasis re-emergence in eliminated foci.^{146,147}

Testing of animals, including tsetse, could become part of the toolbox for post-elimination monitoring to ensure sustained zero-transmission in controlled foci. It is therefore crucial to develop sensitive and *T brucei gambiense*-specific tools for such purpose.

as tsetse habitats, travelling in vehicles with screens or closed windows, wearing clothes with long sleeves, and not wearing dark colours (especially blue and black). Insect repellents provide little protection.

In the context of steady progress against human African trypanosomiasis (85% reduction in cases reported in the past 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 *T brucei gambiense* disease make the interruption of transmission possible (WHO target for 2030). By contrast, the interruption of *T brucei rhodesiense* transmission does not seem attainable with the available tools.

Despite recent advances, the elimination process faces many challenges: sustaining the commitment of national authorities, partners and donors; overcoming the limitations of the current diagnostic and treatment tools; integrating disease control in peripheral health facilities; reaching populations living in or fleeing from areas of civil unrest; clarifying the role of and, if necessary, addressing the asymptomatic human carriers and the possible animal reservoir of *T brucei gambiense*; and, further developing tools and criteria to monitor, verify, and validate disease elimination at different geographical scales.

Conclusions

Human African trypanosomiasis has long been a typical neglected tropical disease, characterised by suboptimal control tools and inadequate funding. Over the past 15 years, thanks to the efforts of a broad range of stakeholders, the situation has changed. Today, human African trypanosomiasis is a rare disease that is targeted for elimination. Drugs are available for free thanks to donations of the manufacturers, low-cost rapid diagnostic tests and vector control tools are on the market; safe oral drugs are expected to become available soon; and, the integration of human African trypanosomiasis diagnosis into peripheral health centres has begun. Yet, disease control might become the victim of its own success. History teaches us that falling case numbers can result in a decline in donor and control agency interest, opening the door to swift and severe recrudescence. Also, the progressive dismantling of highly specialised mobile teams entails the loss of expertise in diagnosis of human African trypanosomiasis, with grave consequences at the individual and community levels.

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

Contributors

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

Declaration of interests

We declare no competing interests.

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