Human African trypanosomiasis

Büscher Philippe PhD[§1], Cecchi Giuliano PhD[2], Jamonneau Vincent PhD[3], Priotto Gerardo MD[4]

[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.

The published journal article is available at: http://dx.doi.org/10.1016/S0140-6736(17)31510-6

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 Africa [1].

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 epidemics [2]. Furthermore, in a globalised world, HAT cases are diagnosed outside African endemic countries among travellers, tourists, expatriates and migrants [3].

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 congenitally [4-6]. 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 colonialism [10]. 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 transmission [11]. 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 environments [14-16]. 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 unclear [17]. 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 continents [3]. 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 insects [20]. These unicellular parasites have co-evolved with their hosts to such an extent that most of them are commensal rather than pathogenic [21]. 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 coat [24]. 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 infections [25-27]. 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 damage [28]. 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 saliva [29].
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 type [30]. *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 forms [37]. 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* HAT [42]. *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 variability [45].

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 night [47-49].

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 progression [50]. 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 relevant [31]. Parasitological confirmation of *gambiense* HAT is achieved by microscopic examination of a lymph node aspirate (https://vimeo.com/200798186, courtesy of Epco 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 blood [79]. 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 puncture [80]. 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 CFS define second stage [31]. 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 cases [83]. 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 countries [84-86]. 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 problems [97].

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 parasite [98-101]. 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 cure [105]. 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 patients [109]. 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 behaviour [110]. 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 diazepam [111]. 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 cases [110]. Cardiac failure is common and may be fatal but it may be attributable also to HAT itself [112].

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 patients [31]. 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 conclusion [115], and a benzoxaborole called SCYX-7158, taken in one single oral dose has entered a phase II/III trial [116].

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 elimination [121].

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 structures [120]. 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 detection [124]. 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.

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.

Acknowledgments

FAO contribution to this study was provided in the framework of the Programme against African Trypanosomosis (PAAT), and supported by the Government of Italy (FAO Project 'Improving food security in sub-Saharan Africa by supporting the progressive reduction of tsetse-transmitted trypanosomosis in the framework of the NEPAD', codes GTFS/RAF/474/ITA and GCP/RAF/502/ITA).

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.

References

1 Simarro PP, Cecchi G, Paone M, Franco JR, Diarra A, Ruiz JA et al. The atlas of human African trypanosomiasis: a contribution to global mapping of neglected tropical diseases. *Int J Health Geogr* 2010; **9**:57.

2 Franco JR, Simarro PP, Diarra A, Jannin JG. Epidemiology of human African trypanosomiasis. *Clin Epidemiol* 2014; **6**:257-75.

3 Simarro PP, Franco JR, Cecchi G, Paone M, Diarra A, Ruiz Postigo JA et al. Human African trypanosomiasis in non-endemic countries (2000-2010). *J Travel Med* 2012; **19**:44-53.

4 Lindner AK, Priotto G. The unknown risk of vertical transmission in sleeping sickness--a literature review. *PLoS Negl Trop Dis* 2010; **4**:e783.

5 Lestrade-Carluer De Kyvon MA, Maakaroun-Vermesse Z, Lanotte P, Priotto G, Perez-Simarro P, Guennoc AM et al. Congenital trypanosomiasis in child born in France to African mother. *Em Inf Dis* 2016 May; **22**:935-7.

6 Rocha G, Martins A, Gama G, Brandão F, Atouguia J. Possible cases of sexual and congenital transmission of sleeping sickness. *Lancet* 2004; **363**:247.

7 Mulumba MA, Kibonge MC, Mulumba MP, Musongela JP, Büscher P. Plaidoyer pour une nouvelle stratégie transfusionelle en zone endémique de la trypanosomiase humaine africaine. *Congo Médical* 2005; **4**:99-106.

8 Herwaldt BL. Laboratory-acquired parasitic infections from accidental exposures. *Clin Microbiol Rev* 2001 October; **14**:659-88.

9 Hira PR, Husein SF. Some transfusion-induced parasitic infections in Zambia. *J Hyg Epidemiol Microbiol Immunol* 1979; **23**:436-44.

10 Lyons M. The colonial disease. A social history of sleeping sicknes in norther Zaire, 1900-1940. Cambridge: Cambridge University Press; 1992.

11 Courtin F, Jamonneau V, Duvallet G, Garcia A, Coulibaly B, Doumenge JP et al. Sleeping sickness in West Africa (1906-2006): changes in spatial repartition and lessons from the past. *Trop Med* 2008 March; **13**:334-44.

12 Diggle PJ. Statistical analysis of spacial point patterns. London: Academic Press; 1983.

13 Cecchi G, Courtin F, Paone M, Diarra A, Franco JR, Mattioli RC et al. Mapping sleeping sickness in Western Africa in a context of demographic transition and climate change. *Parasite* 2009 June; **16**:99-106.

14 Courtin F, Dupont S, Zeze DG, Jamonneau V, Sane B, Coulibaly B et al. Human African trypanosomiasis: urban transmission in the focus of Bonon (Cote d'Ivoire). *Trop Med Int Health* 2005 April; **10**:340-6.

15 Robays J, Ebeja KA, Lutumba P, Miaka mia BC, Kande Betu KM, V, De DR et al. Human African trypanosomiasis amongst urban residents in Kinshasa: a case-control study. *Trop Med Int Health* 2004 August; **9**:869-75.

16 Bilonda Mpiana A, Kabengele Mpinga E, Bukasa Tshilondan JC, Chastonay P, Ilunga wa Kyhi M, Bukonda NKZ et al. Risk factors of human African typanosomiasis in Mbuji Mayi, Eastern Kasai Province, Democratic Republic of the Congo. *International Journal of Tropical Disease & Health* 2015; **5**:190-208.

17 Njiokou F, Nimpaye H, Simo G, Njitchouang GR, Asonganyi T, Cuny G et al. Domestic animals as potential reservoir hosts of *Trypanosoma brucei gambiense* in sleeping sickness foci in Cameroon. *Parasite* 2010; **17**:61-6.

18 Sudarshi D, Lawrence S, Pickrell WO, Eligar V, Walters R, Quaderi S et al. Human African trypanosomiasis Presenting at Least 29 Years after Infection-What Can This Teach Us about the Pathogenesis and Control of this neglected tropical disease? *PLoS Negl Trop Dis* 2014 December; **8**:e3349.

19 Fromentin H. Nouvelles précision sur le Trypanosome sp souche FEO. *Ann Soc Belg Méd Trop* 1963; **5**:797-800.

20 Hoare CA. The trypanosomes of mammals. Oxford: Blackwell Scientific Publications; 1972.

21 Steverding D. The history of African trypanosomiasis. *Parasit Vectors* 2008; **1**:3.

22 Pays E, Vanhollebeke B, Uzureau P, Lecordier L, Perez-Morga D. The molecular arms race between African trypanosomes and humans. *Nat Rev Microbiol* 2014 August; **12**:575-84.

23 Vanhollebeke B, Pays E. The trypanolytic factor of human serum: many ways to enter the parasite, a single way to kill. *Mol Microbiol* 2010 May; **76**:806-14.

24 Horn D. Antigenic variation in African trypanosomes. *Mol Biochem Parasitol* 2014 July; **195**:123-9.

25 Bisser S, Ayed Z, Bouteille B, Stanghellini A, Breton JC, Dumas M et al. Central nervous system involvement in African trypanosomiasis: presence of anti-galactocerebroside antibodies in patients' cerebrospinal fluid. *Trans R Soc Trop Med Hyg* 2000; **94**:225-6.

26 Lejon V, Büscher P, Magnus E, Moons A, Wouters I, Van Meirvenne N. A semi-quantitative ELISA for detection of *Trypanosoma brucei gambiense* specific antibodies in serum and cerebrospinal fluid of sleeping sickness patients. *Acta Trop* 1998; **69**:151-64.

27 Lejon V, Mumba Ngoyi D, Ilunga M, Beelaert G, Maes I, Büscher P et al. Low specificities of HIV diagnostic tests caused by *Trypanosoma brucei gambiense* sleeping sickness. *J Clin Microbiol* 2010; **48**:2836-9.
28 Kristensson K, Masocha W, Bentivoglio M. Mechanisms of CNS invasion and damage by parasites. *Handb Clin Neurol* 2013; **114**:11-22.
29 Stijlemans B, Caljon G, Van Den Abbeele J, Van Ginderachter JA, Magez S, De TC. Immune evasion strategies of *Trypanosoma brucei* within the mammalian host: progression to pathogenicity. *Front Immunol* 2016; **7**:233.
30 Cecchi G, Mattioli RC, Slingenbergh J, de La Rocque S. Land cover and tsetse fly distributions in sub-Saharan Africa. *Med Vet Entomol* 2008 December; **22**:364-73.
31 World Health Organization. Control and surveillance of human African trypanosomiasis. 2013;984Available from: URL: http://apps.who.int/iris/bitstream/10665/95732/1/9789241209847_eng.pdf
32 Grébaut P, Melachio T, Nyangmang S, Eyenga VE, Njitchouang GR, Ofon E et al. Xenomonitoring of sleeping sickness transmission in Campo (Cameroon). *Parasit Vectors* 2016 April 12; **9**:201.
33 Solano P, Torr SJ, Lehane MJ. Is vector control needed to eliminate *gambiense* human African trypanosomiasis? *Front Cell Infect Microbiol* 2013; **3**:33.
34 Shereni W, Anderson NE, Nyakupinda L, Cecchi G. Spatial distribution and trypanosomal infection of tsetse flies in the sleeping sickness focus of Zimbabwe (Zambezi escarpment, Hurungwe District). *Parasit Vectors* 2016; **9**:605.
35 Capewell P, Cren-Travaillé C, Marchesi F, Johnston P, Clucas C, Benson A et al. The skin is a significant but overlooked anatomical reservoir for vector-borne African trypanosomes. *eLIFE* 2016; **10**:17716.
36 Caljon G, Van Reet N, De Trez C, Vermeersch M, Pérez-Morga D, Van Den Abbeele J. The dermis as a delivery site of *Trypanosoma brucei f*or tsetse flies. *PLoS Pathog* 2016; **12**:e1005744.
37 Ooi CP, Bastin P. More than meets the eye: understanding *Trypanosoma brucei* morphology in the tsetse. *Front Cell Infect Microbiol* 2013; **3**:71.
38 Auty H, Anderson NE, Picozzi K, Lembo T, Mubanga J, Hoare R et al. Trypanosome diversity in wildlife species from the Serengeti and Luangwa Valley ecosystems. *PLoS Negl Trop Dis* 2012; **6**:e1828.
39 Jamonneau V, Ravel S, Koffi M, Kaba D, Zeze DG, Ndri L et al. Mixed infections of trypanosomes in tsetse and pigs and their epidemiological significance in a sleeping sickness focus of Côte d'Ivoire. *Parasitology* 2004; **129**:693-702.
40 MacLean LM, Odiit M, Chisi JE, Kennedy PG, Sternberg JM. Focus-specific clinical profiles in human African trypanosomiasis caused by *Trypanosoma brucei rhodesiense*. *PLoS Negl Trop Dis* 2010; **4**:e906.
41 Van Marck EA, Gigase PL, Beckers A, Wéry M. Experimental infections of laboratory rodents with recently isolated stocks of *Trypanosoma brucei gambiense*. 2. Histopathological investigations. *Z Parasitenkd* 1981; **64**:187-93.
42 Jamonneau V, Ilboudo H, Kaboré J, Kaba D, Koffi M, Solano P et al. Untreated infections by *Trypanosoma brucei gambiense* are not 100% fatal. *PLoS Negl Trop Dis* 2012; **6**:e1691.
43 Odiit M, Kanshme F, Enyaru JCK. Duration of symptoms and case fatality of sleeping sickness caused by *Trypansoma brucei rhodesiense* in Tororo, Uganda. *East Afr Med J* 1997; **74**:792-5.
44 Checchi F, Filipe JAN, Barrett MP, Chandramohan D. The natural progression of *gambiense* sleeping sickness: What is the evidence? *PLoS Negl Trop Dis* 2008; **2**:e303.
45 Checchi F, Filipe JAN, Haydon DT, Chandramohan D, Chappuis F. Estimates of the duration of the early and late stage of *gambiense* sleeping sickness. *BMC Infect Dis* 2008; **8**:doi:10.1186/1471-2334-8-16.
46 Küpfer I, Hhary EP, Allan M, Edielu A, Burri C, Blum JA. Clinical presentation of *T.b. rhodesiense* sleeping sickness in second stage patients from Tanzania and Uganda. *PLoS Negl Trop Dis* 2011; **5**:e968.
47 Buguet A, Bourdon L, Bouteille B, Cespuglio R, Vincendeau P, Radomski MW et al. The duality of sleeping sickness: focusing on sleep. *Sleep Med Rev* 2001; **5**:139-53.
48 Mpandzou G, Cespuglio R, Ngampo S, Bandzouzi B, Bouteille B, Vincendeau P et al. Polysomnography as a diagnosis and post-treatment follow-up tool in human African trypanosomiasis: a case study in an infant. *J Neurol Sci* 2011 June 15; **305**:112-5.
49 Njamnshi AK, Seke Etet PF, Perrig S, Acho A, Funsha JY, Mumba D et al. Actigraphy in human African trypanosomiasis as a tool for objective clinical evaluation and monitoring: a pilot study. *PLoS Negl Trop Dis* 2012; **6**:e1525.
50 Blum J, Schmid C, Burri C. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. *Acta Trop* 2006; **97**:55-64.
51 Blum JA, Schmid C, Burri C, Hatz C, Olson C, Fungula B et al. Cardiac alterations in human African trypanosomiasis (*T.b. gambiense*) with respect to the disease stage and antiparasitic treatment. *PLoS Negl Trop Dis* 2009; **3**:e383.-doi:10.1371/journal.pntd.0000383.
52 Blum JA, Zellweger MJ, Burri C, Hatz Ch. Cardiac involvement in African and American trypanosomiasis. *Lancet Infect Dis* 2008; **8**:631-41.

53 Kato CD, Nanteza A, Mugasa C, Edyelu A, Matovu E, Alibu VP. Clinical profiles, disease outcome and co-morbidities among *T. b. rhodesiense* sleeping sickness patients in Uganda. *PLoS ONE* 2015; **10**:e0118370.
54 Kouchner G, Bouree P, Lowenthal M. [Hepatic involvement in *Trypanosoma rhodesiense* trypanosomiasis]. *Bull Soc Pathol Exot Filiales* 1979 March; **72**:131-5.
55 Urech K, Neumayr A, Blum J. Sleeping sickness in travelers - do they really sleep? *PLoS Negl Trop Dis* 2011 November; **5**:e1358.
56 Duggan AJ, Hutchinson MP. Sleeping sickness in europeans: a review of 109 cases. *J Trop Med Hyg* 1966; **69**:124-31.
57 Oscherwitz SL. East African trypanosomiasis. *J Travel Med* 2003 March; **10**:141-3.
58 Magnus E, Van Meirvenne N, Vervoort T, Le Ray D, Wéry M. Use of freeze-dried trypanosomes in the indirect fluorescent antibody test for the serodiagnosis of sleeping sickness. *Ann Soc Belg Méd Trop* 1978; **58**:103-9.
59 Lejon V, Büscher P. Serological diagnosis. In: Cattand P, Louis FJ, Simarro PP, editors. Sleeping Sickness Lectures.Gémenos: Association contre la Trypanosomiase en Afrique; 2013. p. 199-214.
60 Büscher P, Mertens P, Leclipteux T, Gilleman Q, Jacquet D, Mumba Ngoyi D et al. Sensitivity and specificity of HAT Sero-K-SeT, a rapid diagnostic test for serodiagnosis of sleeping sickness caused by *Trypanosoma brucei gambiense*: a case-control study. *The Lancet Global Health* 2014; **2**:e359-e363.
61 Büscher P, Gilleman Q, Lejon V. Novel rapid diagnostic test for sleeping sickness. *N Engl J Med* 2013; **368**:1069-70.
62 Bisser S, Lumbala C, Nguertoum E, Kande V, Flevaud L, Vatunga G et al. Sensitivity and specificity of a prototype rapid diagnostic test for the detection of *Trypanosoma brucei gambiense* infection: a multi-centric prospective study. *PLoS Negl Trop Dis* 2016; **10**:e0004608.
63 Jamonneau V, Bucheton B. The challenge of serodiagnosis of sleeping sickness in the context of elimination. *Lancet Glob Health* 2014 June; **2**:e306-e307.
64 Peeling RW, Holmes KK, Mabey D, Rondon A. Rapid tests for sexually transmitted infections (STIs): the way forward. *Sex Transm Dis* 2006; **82 Suppl V**:v1-v6.
65 Sullivan L, Fleming J, Sastry L, Mehlert A, Wall SJ, Ferguson MAJ. Identification of sVSG117 as an immunodiagnostic antigen and evaluation of a dual-antigen lateral flow test for the diagnosis of human African trypanosomiasis. *PLoS Negl Trop Dis* 2014; **8**:e2976.
66 Sternberg JM, Gierlinski M, Biéler S, Ferguson MA, Ndung'u JM. Evaluation of the diagnostic accuracy of prototype rapid tests for human African trypanosomiasis. *PLoS Negl Trop Dis* 2014 December; **8**:e3373.
67 Rooney B, Piening T, Büscher P, Rogé S, Smales M. Expression of *Trypanosoma brucei gambiense* antigens in *Leishmania tarentolae*. Potential for rapid serodiagnostic tests (RDTs). *PLoS Negl Trop Dis* 2015; **9**:e0004271.
68 Jamonneau V, Camara O, Ilboudo H, Peylhard M, Koffi M, Sakande H et al. Accuracy of individual rapid tests for serodiagnosis of *gambiense* sleeping sickness in West Africa. *PLoS Negl Trop Dis* 2015 February; **9**:e0003480.
69 Zhou X-H, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine. New York: John Wiley and Sons; 2002.
70 Camara O, Camara M, Lejon V, Ilboudo H, Sakande H, Léno M et al. Immune trypanolysis test with blood spotted on filter paper for epidemiological surveillance of sleeping sickness. *Trop Med Int Health* 2014; **19**:828-31.
71 Van Meirvenne N, Magnus E, Büscher P. Evaluation of variant specific trypanolysis tests for serodiagnosis of human infections with *Trypanosoma brucei gambiense*. *Acta Trop* 1995; **60**:189-99.
72 Guedegbe B, Verhulst A, Van Meirvenne N, Pandey VS, Doko A. Indications sérologiques de l'existence d'un réservoir sauvage du *Trypanosoma brucei gambiense* dans la réserve de la biosphère de la Pendjari en République du Bénin. *Ann Soc Belg Méd Trop* 1992; **72**:113-20.
73 Kagbadouno MS, Camara M, Rouamba J, Rayaisse JB, Traore IS, Camara O et al. Epidemiology of sleeping sickness in Boffa (Guinea): where are the trypanosomes? *PLoS Negl Trop Dis* 2012; **6**:e1949.
74 Büscher P, Mumba Ngoyi D, Kaboré J, Lejon V, Robays J, Jamonneau V et al. Improved models of mini anion exchange centrifugation technique (mAECT) and modified single centrifugation (MSC) for sleeping sickness diagnosis and staging. *PLoS Negl Trop Dis* 2009; **3**:e471.
75 Camara M, Camara O, Ilboudo H, Sakande H, Kaboré J, N'Dri L et al. Sleeping sickness diagnosis: use of buffy coats improves the sensitivity of the mini anion exchange centrifugation test. *Trop Med Int Health* 2010; **15**:796-9.
76 Miézan TW, Meda AH, Doua F, Djé NN, Lejon V, Büscher P. Single centrifugation of cerebrospinal fluid in a sealed pasteur pipette for simple, rapid and sensitive detection of trypanosomes. *Trans R Soc Trop Med Hyg* 2000; **94**:293.
77 Woo PTK. The haematocrit centrifuge technique for the diagnosis of African trypanosomiasis. *Acta Trop* 1970; **27**:384-6.

78 World Health Organization. Trypanosomiasis control manual. Geneva: African Medical and Research Foundation Nairobi, Kenya; 1983.
79 Mumba Ngoyi D, Ali Ekangu R, Mumvemba Kodi MF, Pyana PP, Balharbi F, Decq M et al. Performance of parasitological and molecular techniques for the diagnosis and surveillance of *gambiense* sleeping sickness. *PLoS Negl Trop Dis* 2014; **8**:e2954.
80 Mumba Ngoyi D, Menten J, Pyana PP, Büscher P, Lejon V. Stage determination in sleeping sickness: comparison of two cell counting and two parasite detection techniques. *Trop Med Int Health* 2013; **18**:778-82.
81 Lejon V, Legros D, Richer M, Ruiz JA, Jamonneau V, Doua F et al. IgM quantification in the cerebrospinal fluid of sleeping sickness patients by a latex card agglutination test. *Trop Med Int Health* 2002; **7**:685-92.
82 Tiberti N, Hainard A, Lejon V, Courtioux B, Matovu E, Enyaru J et al. Cerebrospinal fluid neopterin as a marker of the meningo-encephalitic stage of *Trypanosoma brucei gambiense* sleeping sickness. *PLoS ONE* 2012; **7**:e40909.
83 Migchelsen SJ, Büscher P, Hoepelman AIM, Schallig HDFH, Adams ER. Human African trypanosomiasis: a review of non-endemic cases in the past 20 years. *Int J Infect Dis* 2011; **15**:e517-e524.
84 Büscher P, Deborggraeve S. How can molecular diagnostics contribute to the elimination of human African trypanosomiasis? *Expert Rev Mol Diagn* 2015; **15**:607-15.
85 Deborggraeve S, Büscher P. Recent progress in molecular diagnosis of sleeping sickness. *Expert Rev Mol Diagn* 2012; **12**:719-30.
86 Deborggraeve S, Lejon V, Ali Ekangu R, Mumba Ngoyi D, Pyana PP, Ilunga M et al. Diagnostic accuracy of PCR in *gambiense* sleeping sickness diagnosis, staging and post-treatment follow-up: a 2-year longitudinal study. *PLoS Negl Trop Dis* 2011; **5**:e972.
87 Cecchi G, Paone M, Feldmann U, Vreysen MJ, Diall O, Mattioli RC. Assembling a geospatial database of tsetse-transmitted animal trypanosomosis for Africa. *Parasit Vectors* 2014 January 21; **7**:39.
88 Cecchi G, Paone M, Argiles HR, Vreysen MJ, Mattioli RC. Developing a continental atlas of the distribution and trypanosomal infection of tsetse flies (Glossina species). *Parasit Vectors* 2015 May 22; **8**:284.
89 Deborggraeve S, Koffi M, Jamonneau V, Bonsu FA, Queyson R, Simarro P et al. Molecular analysis of archived blood slides reveals an atypical human *Trypanosoma* infection. *Diagn Microbiol Infect Dis* 2008; **61**:428-33.
90 Anderson NE, Mubanga J, Fèvre EM, Picozzi K, Eisler MC, Thomas R et al. Characterisation of the wildlife reservoir community for human and animal trypanosomiasis in the Luangwa Valley, Zambia. *PLoS Negl Trop Dis* 2011 June; **5**:e1211.
91 Cordon-Obras C, Rodriguez YF, Fernandez-Martinez A, Cano J, Ndong-Mabale N, Ncogo-Ada P et al. Molecular evidence of a *Trypanosoma brucei gambiense* sylvatic cycle in the human african trypanosomiasis foci of Equatorial Guinea. *Front Microbiol* 2015; **6**:765.
92 Truc P, Büscher P, Cuny G, Gonzatti MI, Jannin J, Joshi PP et al. Atypical human infections by animal trypanosomes. *PLoS Negl Trop Dis* 2013; **7**:e2256.
93 Cordon-Obras C, Garcia-Estebanez C, Ndong-Mabale N, Abaga S, Ndongo-Asumu P, Benito A et al. Screening of *Trypanosoma brucei gambiense* in domestic livestock and tsetse flies from an insular endemic focus (Luba, Equatorial Guinea). *PLoS Negl Trop Dis* 2010; **4**:e704.
94 Radwanska M, Claes F, Magez S, Magnus E, Perez-Morga D, Pays E et al. Novel primer sequences for a polymerase chain reaction-based detection of *Trypanosoma brucei gambiense*. *Am J Trop Med Hyg* 2002; **67**:289-95.
95 Radwanska M, Chamekh M, Vanhamme L, Claes F, Magez S, Magnus E et al. The serum resistance-associated gene as a diagnostic tool for the detection of *Trypanosoma brucei rhodesiense*. *Am J Trop Med Hyg* 2002; **67**:684-90.
96 Simarro PP, Franco J, Diarra A, Postigo JA, Jannin J. Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis. *Parasitology* 2012 June; **139**:842-6.
97 Pohlig G, Bernhard SC, Blum J, Burri C, Mpanya A, Lubaki JP et al. Efficacy and safety of pafuramidine versus pentamidine maleate for treatment of first stage sleeping sickness in a randomized, comparator-controlled, international phase 3 clinical trial. *PLoS Negl Trop Disi* 2016 February; **10**:e0004363.
98 Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009 June 24; **374**:56-64.
99 Franco JR, Simarro PP, Dia A, Ruiz-Postigo JA, Samo M, Jannin JG. Monitoring the use of nifurtimox-eflornithine combination therapy (NECT) in the treatment of second stage *gambiense* human African trypanosomiasis. *Research and Reports in Tropical Medicine* 2012; **3**:93-101.
100 Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage human African trypanosomiasis. *Cochrane Database Syst Rev* 2013 June 28; CD006201.

101 Alirol E, Schrumpf D, Amici HJ, Riedel A, de PC, Quere M et al. Nifurtimox-eflornithine combination therapy for second-stage gambiense human African trypanosomiasis: Medecins Sans Frontieres experience in the Democratic Republic of the Congo. *Clin Infect Dis* 2013 January; **56**:195-203.
102 Checchi F, Piola P, Ayikoru H, Thomas F, Legros D, Priotto G. Nifurtimox plus eflornithine for late-stage sleeping sickness in Uganda: a case series. *PLoS Negl Trop Dis* 2007; **1**:e64.
103 Priotto G, Fogg C, Balasegaram M, Erphas O, Louga A, Checchi F et al. Three drug combinations for late-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Uganda. *PLoS Clinical Trials* 2006; **1**:1-8.
104 Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for *T. b. gambiense* sleeping sickness. *PLoS Negl Trop Dis* 2012; **6**:e1920.
105 Bitonti AJ, Bacchi CJ, McCann PP, Sjoerdsma A. Uptake of alpha-difluoromethylornithine by *Trypanosoma brucei brucei*. *Biochem Pharmacol* 1986; **35**:351-4.
106 Balasegaram M, Harris S, Checchi F, Hamel C, Karunakara U. Treatment outcomes and risk factors for relapse in patients with early-stage human African trypanosomiasis (HAT) in the Republic of the Congo. *Bull World Health Organ* 2006; **84**:777-82.
107 Priotto G, Pinoges L, Badi Fursa I, Burke B, Nicolay N, Grillet G et al. Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *Br Med J* 2008; **336**:705-8.
108 Chappuis F, Udayraj N, Stietenroth K, Meussen A, Bovier PA. Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. *Clin Infect Dis* 2005; **41**:748-51.
109 Seixas JBA. Investigation on the encephalopathic syndrome during melarsoprol treatment of human African trypanosomiasis Universidade Nova de Lisboa, University of Basel; 2004.
110 Pépin J, Milord F, Khonde A, Niyonsenga T, Loko L, Mpia B. Gambiense trypanosomiasis: frequency of, and risk factors for, failure of melarsoprol therapy. *Trans R Soc Trop Med Hyg* 1994; **88**:447-52.
111 Brun R, Blum J, Chappuis F, Burri C. Human African trypanosomiasis. *Lancet* 2010 January 9; **375**:148-59.
112 Adams JH, Haller L, Boa YF, Doua F, Dago A, Konian K. Human African trypanosomiasis (*T.b. gambiense*): a study of 16 fatal cases of sleeping sickness with some observation on acute reactive arsenical encephalopathy. *Neuropathol Appl Neurobiol* 1986; **12**:81-94.
113 Graf FE, Ludin P, Wenzler T, Kaiser M, Brun R, Pyana PP et al. Aquaporin 2 mutations in *Trypanosoma brucei gambiense* field isolates concur with decreased susceptibility to pentamidine and melarsoprol. *PLoS Negl Trop Dis* 2013; **7**:e2475.
114 Munday JC, Eze AA, Baker N, Glover L, Clucas C, Aguinaga Andrés D et al. *Trypanosoma brucei* aquaglyceroporin 2 is a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs and the main genetic determinant of resistance to these drugs. *J Antimicrob Chemother* 2014 March; **69**:651-63.
115 Tarral A, Blesson S, Mordt OV, Torreele E, Sassella D, Bray MA et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. *Clin Pharmacokinet* 2014 June; **53**:565-80.
116 Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, Sligar JM et al. SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. *PLoS Negl Trop Dis* 2011 June; **5**:e1151.
117 Cecchi G, Paone M, Franco JR, Fèvre EM, Diarra A, Ruiz JA et al. Towards the Atlas of human African trypanosomiasis. *Int J Health Geogr* 2009 March 18; **8**:15.
118 Lumbala C, Simarro PP, Cecchi G, Paone M, Franco JR, Kande Betu KM, V et al. Human African trypanosomiasis in the Democratic Republic of the Congo: disease distribution and risk. *Int J Health Geogr* 2015; **14**:20.
119 Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA et al. Estimating and mapping the population at risk of sleeping sickness. *PLoS Negl Trop Dis* 2012; **6**:e1859.
120 Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA et al. Mapping the capacities of fixed health facilities to cover people at risk of *gambiense* human African trypanosomiasis. *Int J Health Geogr* 2014 February 11; **13**:4.
121 Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Priotto G et al. Monitoring the progress towards the elimination of *gambiense* human African trypanosomiasis. *PLoS Negl Trop Dis* 2015 June; **9**:e0003785.
122 Mpanya A, Hendrickx D, Vuna M, Kanyinda A, Lumbala C, Tshilombo V et al. Should I get screened for sleeping sickness? A qualitative study in Kasai province, Democratic Republic of Congo. *PLoS Negl Trop Dis* 2012 January; **6**:e1467.
123 Hasker E, Lutumba P, Chappuis F, Kande V, Potet J, De WA et al. Human African trypanosomiasis in the democratic republic of the congo: a looming emergency? *PLoS Negl Trop Dis* 2012 December; **6**:e1950.

124 Koffi M, N'Djetchi M, Ilboudo H, Kaba D, Coulibaly B, N'Gouan E et al. A targeted door-to-door strategy for sleeping sickness detection in low-prevalence settings in Cote d'Ivoire. *Parasite* 2016; **23**:51.
125 Hasker E, Lumbala C, Mpanya A, Mbo F, Snijders R, Meheus F et al. Alternative strategies for case finding in human African trypanosomiasis in the Democratic Republic of Congo. European Congress on Tropical Medicine and International Health. 6-10/09/2015, Basel, Switzerland. *Trop Med Int Health* 2015; **20**:339.
126 Mitashi PM. Novel diagnostic tests for human African trypanosomiasis: what is their role in primary health care services? University of Antwerp; 2014.
127 Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Jannin JG. The journey towards elimination of *gambiense* human African trypanosomiasis: not far, nor easy. *Parasitology* 2014 May; **141**:748-60.
128 Kambire R, Lingue K, Courtin F, Sidibe I, Kiendrebeogo D, N'gouan KE et al. La Trypanosomose Humaine Africaine dans l'espace ivoiro-burkinabé : optimisation des stratégies de surveillance épidémiologique. *Parasite* 2012 November; **19**:389-96.
129 Courtin F, Camara M, Rayaisse JB, Kagbadouno M, Dama E, Camara O et al. Reducing human-tsetse contact significantly enhances the efficacy of sleeping sickness active screening campaigns: a promising result in the context of elimination. *PLoS Negl Trop Dis* 2015; **9**:e0003727.
130 Shaw AP, Wint GR, Cecchi G, Torr SJ, Mattioli RC, Robinson TP. Mapping the benefit-cost ratios of interventions against bovine trypanosomosis in Eastern Africa. *Prev Vet Med* 2015 December 1; **122**:406-16.
131 Shaw AP, Torr SJ, Waiswa C, Cecchi G, Wint GR, Mattioli RC et al. Estimating the costs of tsetse control options: an example for Uganda. *Prev Vet Med* 2013 July 1; **110**:290-303.
132 Wendo C. Uganda revises cattle treatment to protect humans from sleeping sickness. *Lancet* 2002; **359**:239.
133 Magona JW, Walubengo J. Mass-treatment and insecticide-spraying of animal reservoirs for emergency control of Rhodesiense sleeping sickness in Uganda. *J Vector Borne Dis* 2011 June; **48**:105-8.
134 Vreysen MJ, Seck MT, Sall B, Bouyer J. Tsetse flies: their biology and control using area-wide integrated pest management approaches. *J Invertebr Pathol* 2013 March; **112 Suppl**:S15-S25.
135 Jamonneau V, Bucheton B, Kaboré J, Ilboudo H, Camara O, Courtin F et al. Revisiting the immune trypanolysis test to optimise epidemiological surveillance and control of sleeping sickness in west Africa. *PLoS Negl Trop Dis* 2010; **4**:e917-4.69.
136 Bucheton B, MacLeod A, Jamonneau V. Human host determinants influencing the outcome of *Trypanosoma brucei gambiense* infections. *Parasite Immunol* 2011 August; **33**:438-47.
137 Ilboudo H, Jamonneau V, Camara M, Camara O, Dama E, Leno M et al. Diversity of response to *Trypanosoma brucei gambiense* infections in the Forecariah mangrove focus (Guinea): perspectives for a better control of sleeping sickness. *Microbes Infect* 2011 October; **13**:943-52.
138 Molyneux DH. Animal reservoirs and Gambian trypanosomiasis. *Ann Soc Belg Med Trop* 1973; **53**:605-18.
139 Simo G, Rayaisse JB. Challenges facing the elimination of sleeping sickness in west and central Africa: sustainable control of animal trypanosomiasis as an indispensable approach to achieve the goal. *Parasit Vectors* 2015; **8**:640.

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 parasite [135-137]. 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 88XP, 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 Medicine International 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
gambiense			
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
rhodesiense			
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

[a] Children < 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

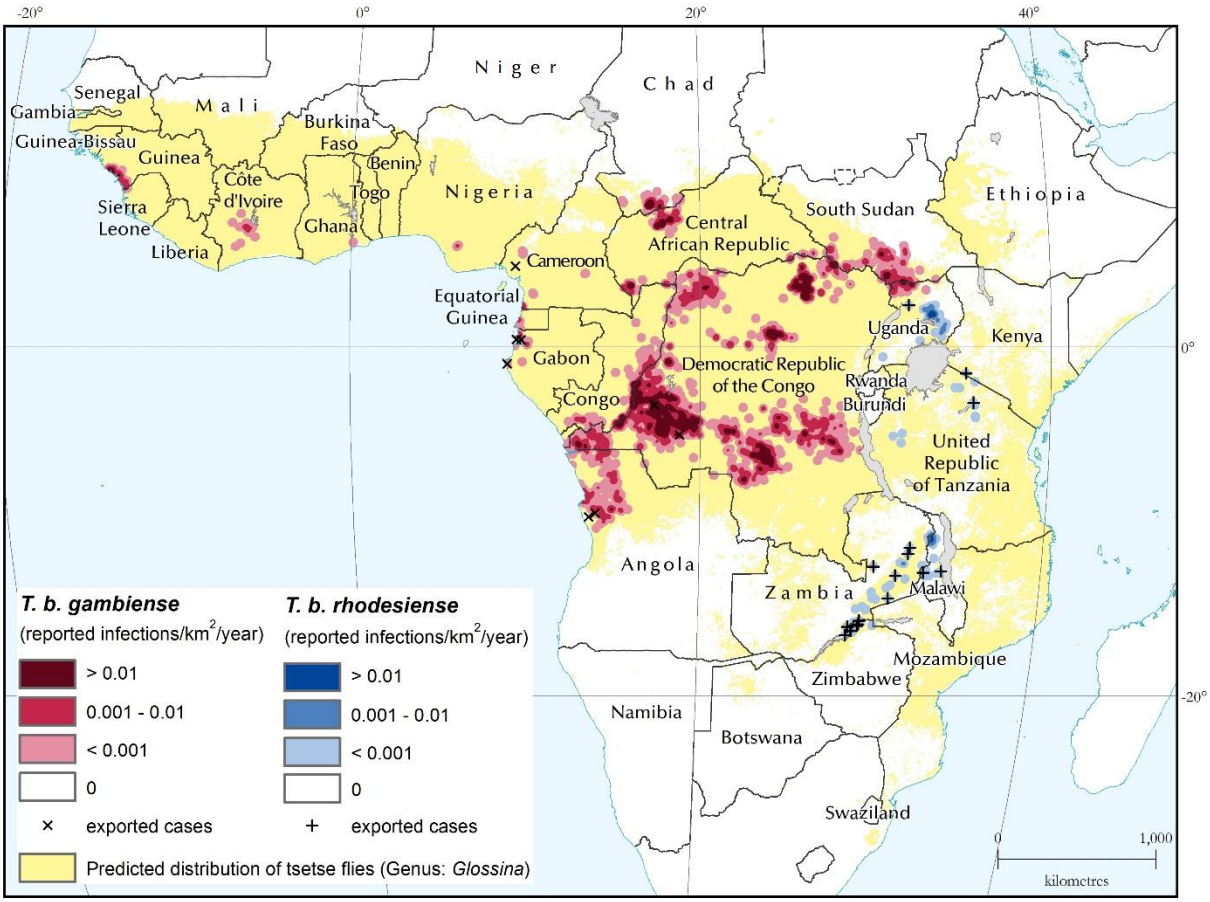

Figure 1: Geographic distribution of reported infections of Human African Trypanosomiasis (Reporting period: 2010-2014).
Gambiense HAT is found in Western and Central Africa, while *rhodesiense* HAT is found in Eastern and Southern Africa. The source of reported infections is the WHO Atlas of HAT [1]. The density of reported infections (i.e. the number of reported infections/km^2/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 Trypanosomosis (http://www.fao.org/ag/againfo/programmes/en/paat/home.html).

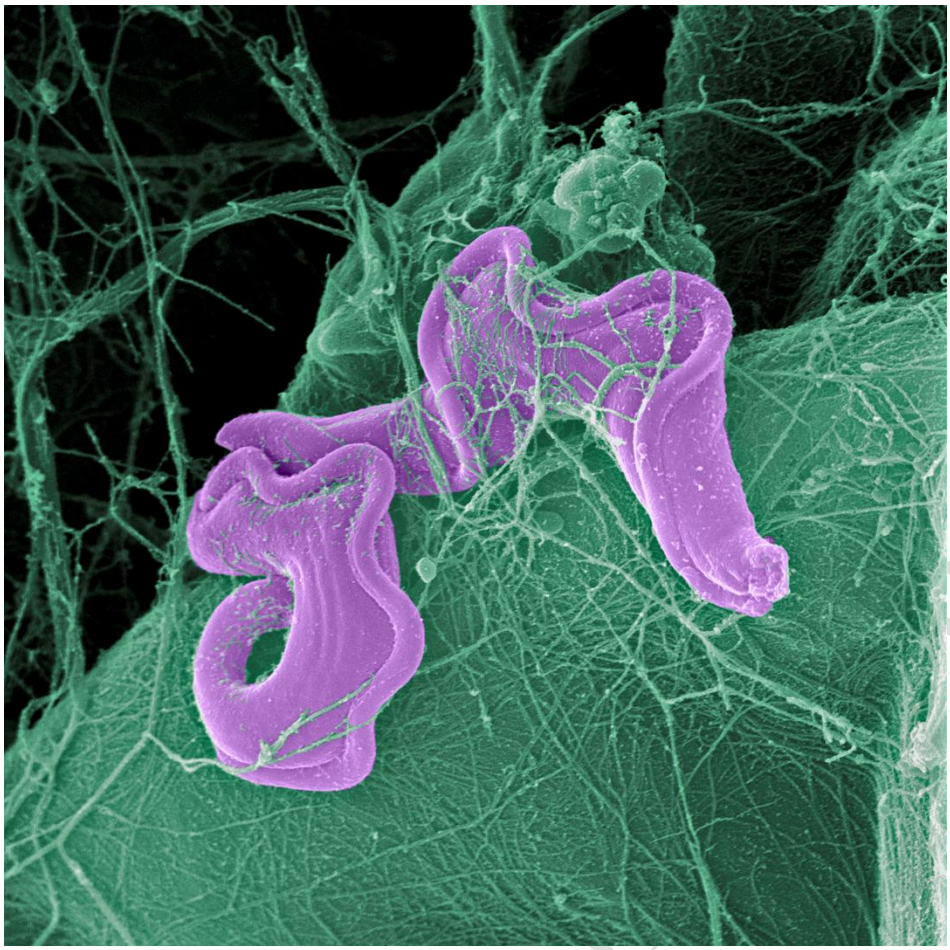

Figure 2: False-colored scanning electronic microscopy image, 14 x 14 microns, showing trypanosomes (purple) and an adipocyte (green) in the ear dermis of a *Trypanosoma brucei* in infected mouse. **Credits:** David Peréz-Morga and Marjorie Vermeersch (Université Libre de Bruxelles), Guy Caljon (Antwerp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

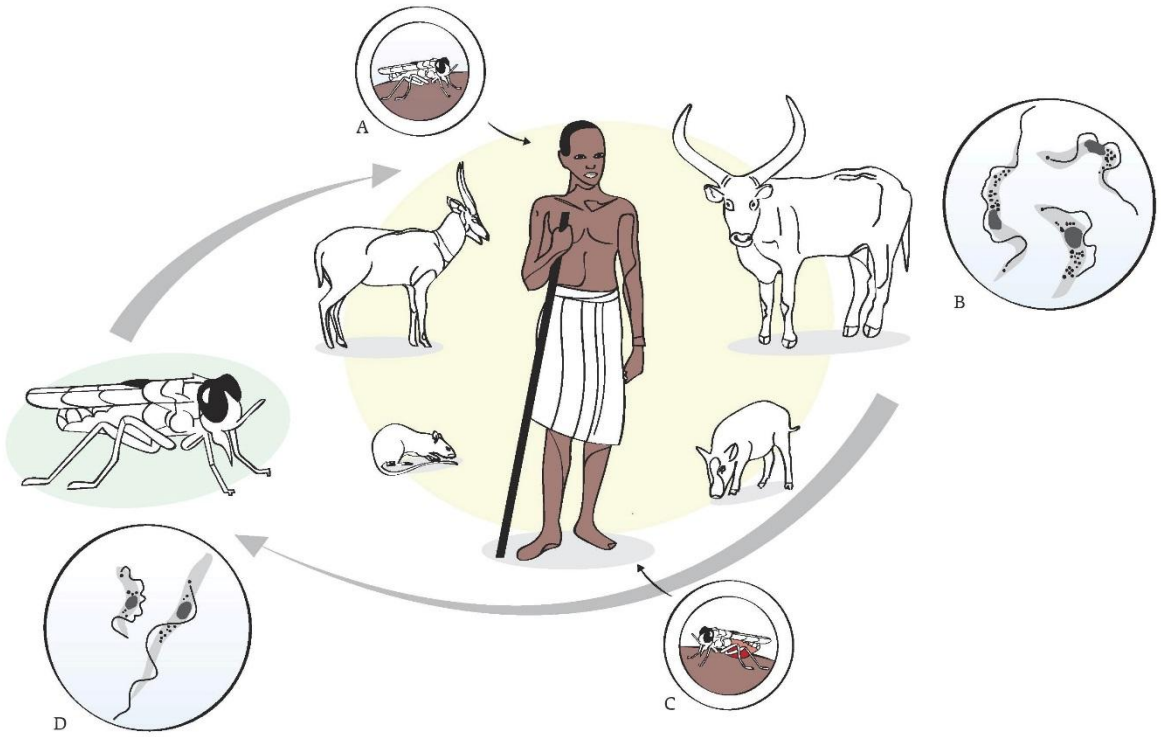

Figure 3: Life cycle of *Trypanosoma brucei*.

(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.

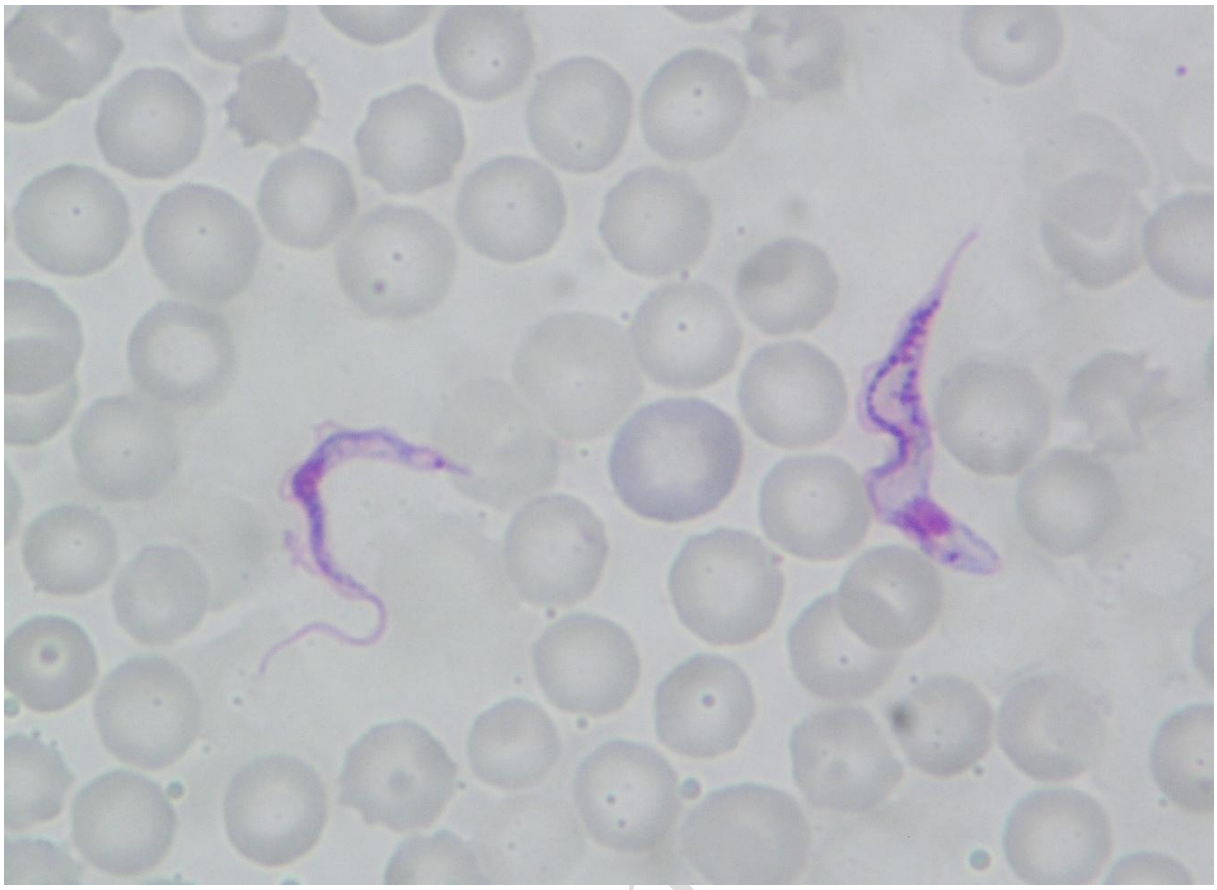

Figure 4: Giemsa stained thin blood film with one long-slender (right side) and one short stumpy trypanosome (left side).

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-myocarditis[51]. 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/µl) 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.