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Human African trypanosomiasis

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Human African trypanosomiasis (sleeping sickness) occurs in sub-Saharan Africa. It is caused by the protozoan parasite *Trypanosoma brucei*, transmitted by tsetse flies. Almost all cases are due to *Trypanosoma brucei gambiense*, which is indigenous to west and central Africa. Prevalence is strongly dependent on control measures, which are often neglected during periods of political instability, thus leading to resurgence. With fewer than 12 000 cases of this disabling and fatal disease reported per year, trypanosomiasis belongs to the most neglected tropical diseases. The clinical presentation is complex, and diagnosis and treatment difficult. The available drugs are old, complicated to administer, and can cause severe adverse reactions. New diagnostic methods and safe and effective drugs are urgently needed. Vector control, to reduce the number of flies in existing foci, needs to be organised on a pan-African basis. WHO has stated that if national control programmes, international organisations, research institutes, and philanthropic partners engage in concerted action, elimination of this disease might even be possible.

Introduction

Human African trypanosomiasis, which is fatal if left untreated, affects rural populations in sub-Saharan Africa. Its prevalence has changed during the past 100 years largely because of control and intervention programmes. After major outbreaks at the beginning of the 19th century, the disease was almost eliminated in the mid-1960s, followed by resurgence in the late 1990s and a fall in the number of cases in recent years. Although the present number of cases (50 000–70 000) seems negligible on a worldwide scale, the characteristics and focal distribution of the disease can have a great socioeconomic effect on affected villages.

Diagnosis and treatment is unsatisfactory and needs more research and development. As one of the most neglected tropical diseases, African trypanosomiasis could catch the attention of initiatives and public–private partnerships. With new methods to diagnose and treat patients and to control transmission by the tsetse fly, elimination of the disease might be possible.

Epidemiology

The geographical range of human African trypanosomiasis (sleeping sickness) is restricted to sub-Saharan Africa (figure 1), where there are suitable habitats for its vector, the tsetse fly. Together with the animal form of African trypanosomiasis, known as *nagana*, human disease is a major cause of rural underdevelopment in sub-Saharan Africa. Although the disease has also been reported in urban and periurban areas,[1] it mainly affects poor and remote rural regions. Disease transmission occurs in children and adults during activities such as farming, hunting, fishing, or washing clothes.

The African trypanosomes pathogenic for man belong to the species *Trypanosoma brucei*, which has three subspecies: *T b gambiense*, which causes endemic disease in central and west Africa; *T b rhodesiense*, which causes more acute disease in east and southern Africa (figure 1); and *T b brucei*, which usually infects domestic and wild animals but not man. The strict geographical separation between *T b gambiense* and *T b rhodesiense* could soon change, however, because the continued spread of *T b rhodesiense* in Uganda towards the northwest might cause an overlap of the distributions of the two forms of disease.[2] Sporadic reports have appeared of disease in man caused by non-human-pathogenic trypanosome species. These species are *T b brucei*,[3] *T congolense*,[4] and *T evansi*.[5]

Three major epidemics have ravaged the continent in the past century.[6] The first, which largely affected equatorial Africa, took place between 1896 and 1906, and killed an estimated 800 000 people.[7] A second major epidemic between 1920 and the late 1940s prompted the colonial powers to invest in vector control and mobile teams to undertake active surveillance of the population—two strategies that are still the pillars of control. These control mechanisms were initially effective, and the disease was almost eradicated in the early 1960s. However, after the advent of independence there was a collapse of surveillance and control activities in most endemic countries, often exacerbated by civil conflicts. This collapse led to a progressive re-emergence of the disease, which reached a peak in the late 1990s in the Democratic Republic of the Congo (DRC), Angola, Central African Republic, southern Sudan, and Uganda (figure 2).[8–14]

Since this peak of infection in the 1990s, increased control activities have succeeded in rolling back disease related to *T b gambiense* in several countries.[15–17] In the 24 countries regarded as endemic for such disease, there was a 69% reduction in the number of reported cases between 1997 and 2006 (from 36 585 to 11 382). However, *T b rhodesiense* disease, which contributed only 4% (n=486)

Search strategy and selection criteria

We did a PubMed search using the keywords: "tsetse", "trypanosomiasis", "trypanosomes", "sleeping sickness", "*T b gambiense*", "*T b rhodesiense*", "treatment", "pentamidine", "suramin", "melarsoprol", "eflornithine", and "DFMO", in various combinations. Additional sources were the Programme against African Trypanosomiasis (PAAT) Tsetse & Trypanosomiasis Information (2005–2008) and personal topic-specific databases of RB and CB.

of all reported cases in 2006, showed no similar decrease because only a few endemic countries implemented control programmes.[18] However, these figures should be regarded with caution since under-reporting is known to mask the true burden of *T b rhodesiense* disease.[19,20] The decrease in reported *T b gambiense* infections is encouraging, but because African trypanosomiasis mainly affects remote rural communities in regions with poor health infrastructures, many cases certainly remain undiagnosed or unreported, and the true burden of disease in Africa remains unknown. WHO used a ratio of 1:3–4 to calculate the figure of 50 000–70 000 new cases in 2004.[21] Hidden pockets of highly endemic *T b gambiense* disease remain, as shown by the high number of patients (n=1800) diagnosed and treated by Médecins Sans Frontières between July, 2007, and June, 2008, in two remote areas of Central African Republic (Batangafo) and DRC (Doruma and Banda) (C F, unpublished data). Similarly, the local burden of *T b rhodesiense* illness on individuals and health services remains high in some affected areas.[22]

Human African trypanosomiasis due to *T b gambiense* is very rare in short-term tourists, but has been reported in immigrants, refugees, and expatriates resident for long periods in rural areas.[23–26] Because of its long incubation time and chronicity, the disease should be considered even if a patient's last stay in an endemic region occurred many years ago. The number of tourists infected in countries that report the most local patients is low, probably because these countries are rarely visited by travellers (figure 1). By contrast, disease due to *T b rhodesiense* has been reported in short-term tourists travelling to east African game reserves, mainly in Tanzania,[27–30] but also in Botswana, Rwanda, Kenya, and Malawi.[31]

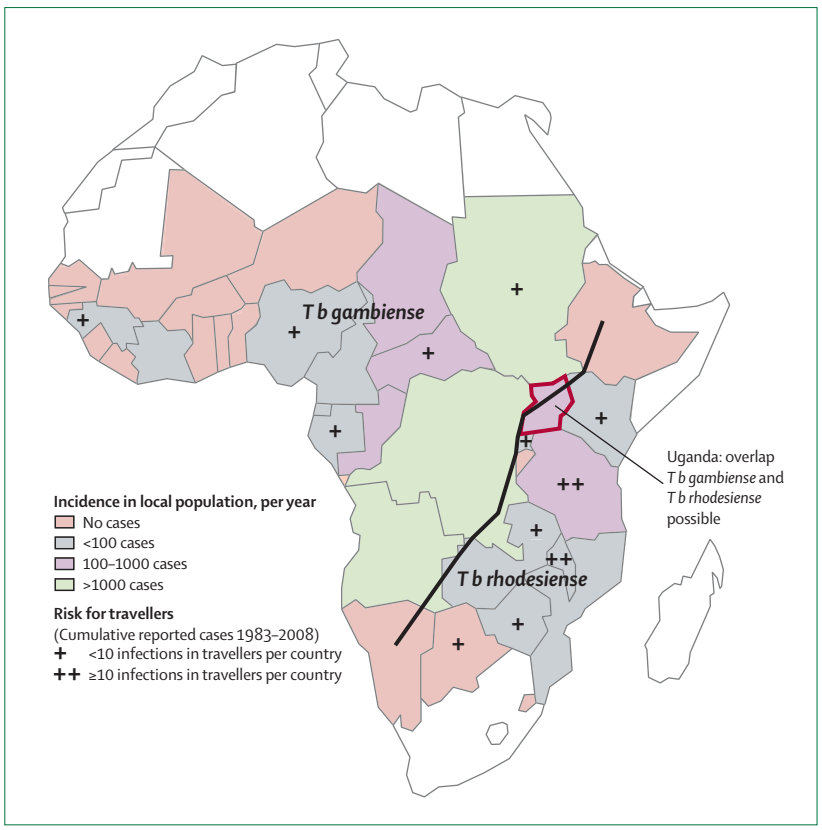


Figure 1: **Distribution of human African trypanosomiasis with incidences and risk for travellers**
The black line divides the areas in which *Trypanosoma brucei gambiense* prevails and those in which *Trypanosoma brucei rhodesiense* predominates (J Blum, Swiss Tropical Institute).

Vector and parasite

Trypanosomes are transmitted by blood-feeding tsetse flies of the genus *Glossina* from one mammalian host to another. Both male and female flies are blood-feeders and can thus bring about transmission. About 30 species and subspecies of tsetse flies exist, and these are separated into three groups that prefer different habitats[32] and show different abilities to transmit *T b gambiense* or *T b rhodesiense* sleeping sickness. The flies' biology has one major peculiarity—they are viviparous. The female fly deposits a fully developed larva, which burrows into the soil, pupates, and emerges as an adult fly a month later. Newly-hatched flies have never been reported to be infected with trypanosomes. The fly first needs to feed on an infected mammalian host, after which the parasites enter the digestive tract. During the following 3–5 weeks they undergo several differentiation steps, including migration to the salivary glands, where they develop into the infective form. The complex process of establishment in the midgut and maturation in the salivary glands depends on many factors, some favouring and others inhibiting its completion (figure 3).[33] Completion of the cycle in the fly is rare in the field, in that only about 0·1% of flies carry a mature infection that can be transmitted when the fly bites another host.

Trypanosomes are unicellular organisms (protozoa) that belong to the family Trypanosomatidae and the genus *Trypanosoma*.[34] The elongated cells are 15–30 µm long and constantly move with the help of a flagellum. They have the cellular organisation of eukaryotic cells, with one tubular mitochondrion that contains the kinetoplast, which is a condensation of the circular mitochondrial DNA. In the initial phase of infection, trypanosomes are restricted to the lymph and blood systems (figure 4). At a later stage they are also seen in brain parenchyma and cerebrospinal fluid (CSF),[35] but are generally extracellular.

Normal human plasma contains a trypanosome lytic factor. This factor destroys trypanosomes pathogenic for animals, whereas *T b gambiense* and *T b rhodesiense* are resistant to it, each by means of a different mechanism.[36] The trypanosome lytic factor has two components, apolipoprotein L1 and haptoglobin-related protein, which are especially active when assembled in one high-density lipoprotein.[37] One reported human infection with *T evansi* might have been attributable to an absence of apolipoprotein L1 in the patient.[38]

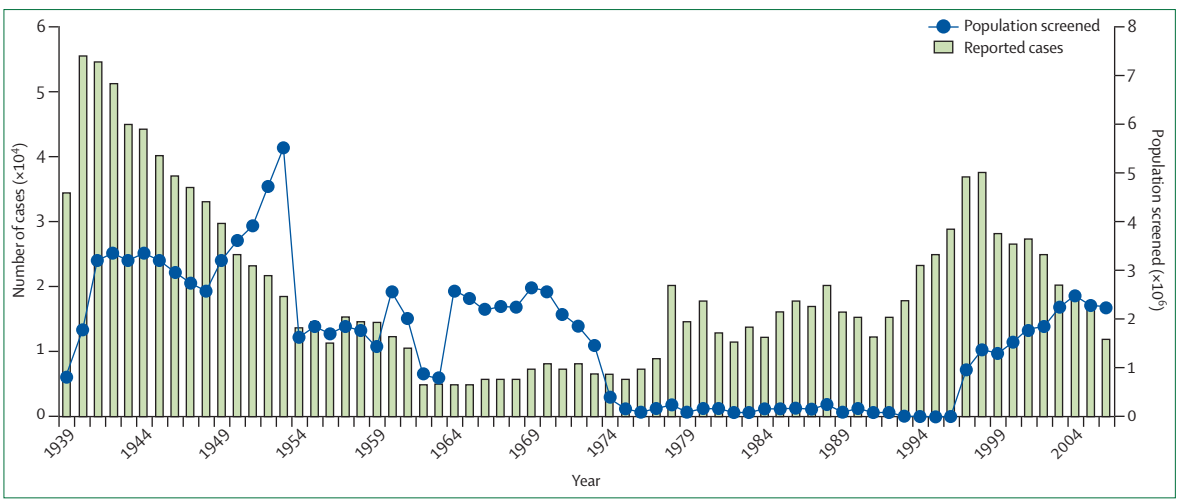


***Figure 2: Trypanosoma brucei gambiense*: comparison between population placed under active surveillance and new cases**
Number of reported cases (columns) and population screened (circles), Africa, 1939–2004. Reproduced under the creative commons licence from reference 6.

Trypanosomes are surrounded by a surface coat composed of a variant surface glycoprotein that protects them from lytic factors in human plasma.[39] When infection occurs, this glycoprotein is recognised by the host's immune system, which starts producing IgM and IgG antibodies. These antibodies neutralise the corresponding trypanosomes, leading to a decrease of parasitaemia. However, a few of the trypanosomes will have changed their surface coats to a new variant surface glycoprotein type that is not affected by the circulating antibodies, so that they can continue to proliferate until new antibodies are produced. This sequence continues, and the immune system is not able to eliminate the parasites. About 2000 variant surface glycoprotein genes, including many pseudogenes, are present in the genome of *T brucei*,[40,41] whereas *T b gambiense* probably has fewer. Only one such glycoprotein is expressed at a specific time. The switch occurs either by transport of a variant surface glycoprotein gene to one of 20 expression sites situated on different telomeres, or by silencing of an active telomere and activation of a telomere on another chromosome. Because of this high degree of antigenic variation, development of a vaccine is unlikely to be feasible.[42]

Domestic and wild animals can also become infected with *T b gambiense*[43] and *T b rhodesiense*. Although they do not fall ill, they have an epidemiological role as carriers or reservoir animals from which tsetse flies can acquire an infection.[44] For *T b rhodesiense*, which is a zoonosis that is usually transmitted from animals to man, cattle are an important reservoir,[45,46] although most wild animals species in game parks can harbour human-pathogenic trypanosomes. For *T b gambiense*, which is anthroponotic—ie, it mostly depends on human-to-human transmission—man provides the main reservoir. Animals play a less important part, but pigs and some wild animal species have been reported as being a reservoir.[47,43]

Clinical features

The disease appears in two stages, the first haemolymphatic stage and the second meningoencephalitic stage, which is characterised by invasion of the CNS. The penetration of trypanosomes through the blood-brain barrier is an active process[48] and occurs at or near intracellular junctions. Disease caused by either of the two parasites leads to coma and death if left untreated. *T b gambiense* infection is characterised by a chronic progressive course. According to models based on survival analysis, the estimated average duration of such infection is around 3 years, which is evenly divided between the first and second stages.[49] *T b rhodesiense* disease is usually acute, and death occurs within weeks or months.[50]

A trypanosomal chancre (a reaction at the location of the tsetse fly bite) is rarely seen with *T b gambiense*, but occurs in 19% of patients infected with *T b rhodesiense*. The leading signs and symptoms of the first stage are chronic and intermittent fever, headache, pruritus, lymphadenopathy, and, to a lesser extent, hepatosplenomegaly. In the second stage, sleep disturbances and neuropsychiatric disorders dominate the clinical presentation.

Fever is intermittent, with attacks lasting from a day to a week, separated by intervals of a few days to a month or longer,[51] and is rarely seen in the second stage.[52] The febrile episodes correspond to a type 1 inflammatory reaction associated with activation of macrophage-1 cells and high concentrations of interferon γ, tumour necrosis factor, reactive oxygen intermediates or metabolites, and nitric oxide. This reaction controls parasite invasion and proliferation, but the exacerbated immune response can induce collateral tissue damage.[53] To alleviate parasite-elicited pathological changes the host can mount type 2 immune responses consisting of sequential production of interleukin 10 and interleukin 4 or interleukin 1 that can induce macrophage-2 cells with anti-inflammatory

properties.[53] The mechanism of antigenic variation on the surface of the parasite allows it to persist and to elicit new parasitic waves.

Sleep disorder is a leading symptom of the second stage and is the one that gave the disease its name. Somnographic studies have shown that the disease causes dysregulation of the circadian rhythm of the sleep/wake cycle and a fragmentation of the sleeping pattern rather than the frequently reported inversion of sleep.[54] In severe cases the circadian rhythm of prolactin, renin, growth hormone, and cortisol secretion disappears.[54,55] The neurological symptoms include tremor, fasciculations, general motor weakness, paralysis of a limb, hemiparesis, akinesia, and abnormal movements such as dyskinesia or chorea-athetosis. There might be Parkinson-like movements due to muscular hypertension, non-specific movement disorders, and speech disorders. Abnormal archaic reflexes can also arise. These disorders are rarely seen during the first stage and increase in frequency with the duration of the disease.[52,56] Psychiatric symptoms such as irritability, psychotic reactions, aggressive behaviour, or inactivity with apathy can dominate the clinical picture.[56] In Europe, infected immigrants have sometimes been wrongly admitted to psychiatric clinics.[57]

Cardiac involvement documented by electrocardiogram (ECG) changes is frequently seen in *T b gambiense* disease, but is rarely of clinical relevance. The most frequent ECG changes are QTc prolongation, repolarisation changes, and low voltage. In *T b rhodesiense* infection, myopericarditis can be more severe.[58,59] By contrast with heart problems in Chagas disease, which is caused by another trypanosome, *T cruzi*, arrhythmias, conduction problems and blocks, and congestive heart failure are rare in African trypanosomiasis.[60,61] Endocrine disorders of the thyroid and adrenocortical function can take the form of hypofunction or hyperfunction, but rarely demand specific treatment.[62] These symptoms are more pronounced in *T b rhodesiense* disease.[63]

The symptomatology of human African trypanosomiasis in travellers is strikingly different from the usual textbook descriptions of African patients, and is similar for both *T b gambiense* and *T b rhodesiense* infections,[51] presenting as an acute febrile disease with temperatures up to 40–41°C.[21,22] In travellers, a chancre at the inoculation site[24] and a trypanosomal rash[22] are more frequently seen, and results of laboratory tests show greater abnormalities than in patients from endemic countries. Severe haematological disorders, impaired kidney function, electrolyte disturbances, high concentrations of C-reactive protein and liver enzymes have been described.[26,27,64,65]

A great diversity of clinical pictures can be seen in patients infected by *T b gambiense*, ranging from acute disease to chronic forms. Asymptomatic carriers are also reported.[66,67] Whereas an initial genetic characterisation of the infecting *T b gambiense* in patients in Côte d'Ivoire showed little genetic polymorphism,[66] a PCR analysis done some years later did detect DNA of *T brucei* sensu lato in healthy carriers. These parasites might represent a distinct and previously unrecognised genetic group of trypanosomes, other than *T b gambiense* or *T b rhodesiense*. An infection or coinfection with these *T brucei* sensu lato could cause a slow and gradual development of morbidity.[68] Additionally, infections of people with trypanosomes thought to be non-pathogenic for man have been described in case reports.[69]

Typically, *T b rhodesiense* disease progresses very rapidly; however, in the southern countries of east Africa, in particular Malawi, a more chronic form has been reported. These two distinct clinical forms have been associated with two genotypes of the SRA gene. Additionally, tumour necrosis factor α concentration was high in early-stage patients in Uganda, whereas in Malawi high concentrations of transforming growth factor β concentrations were seen.[70] However, the apparently

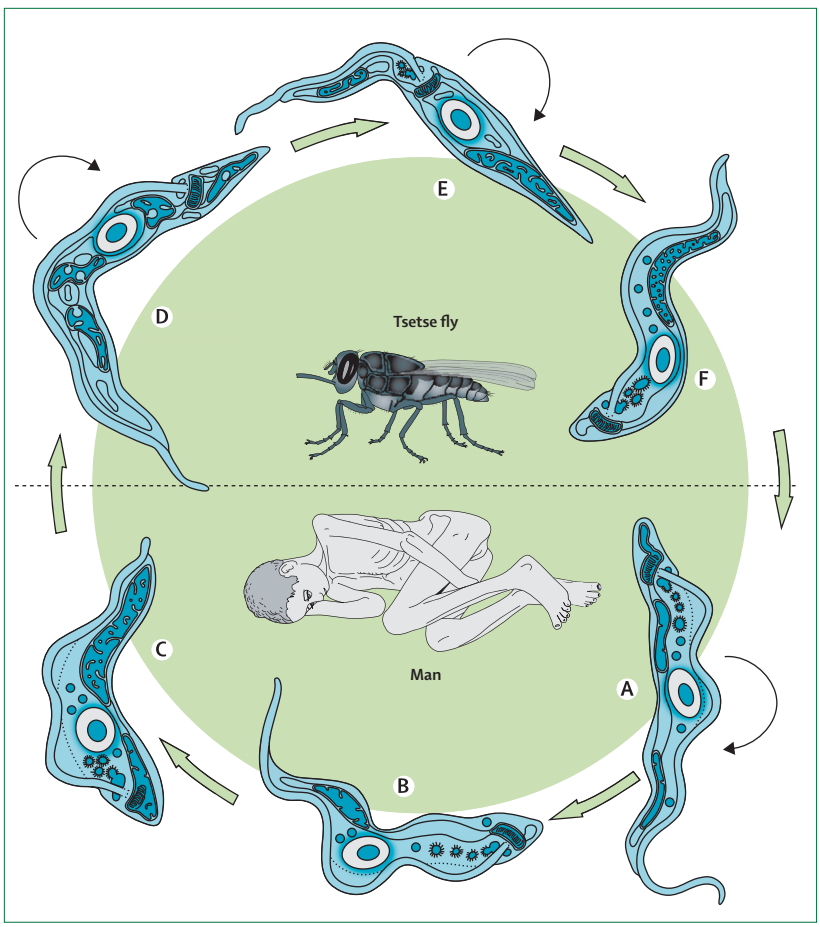
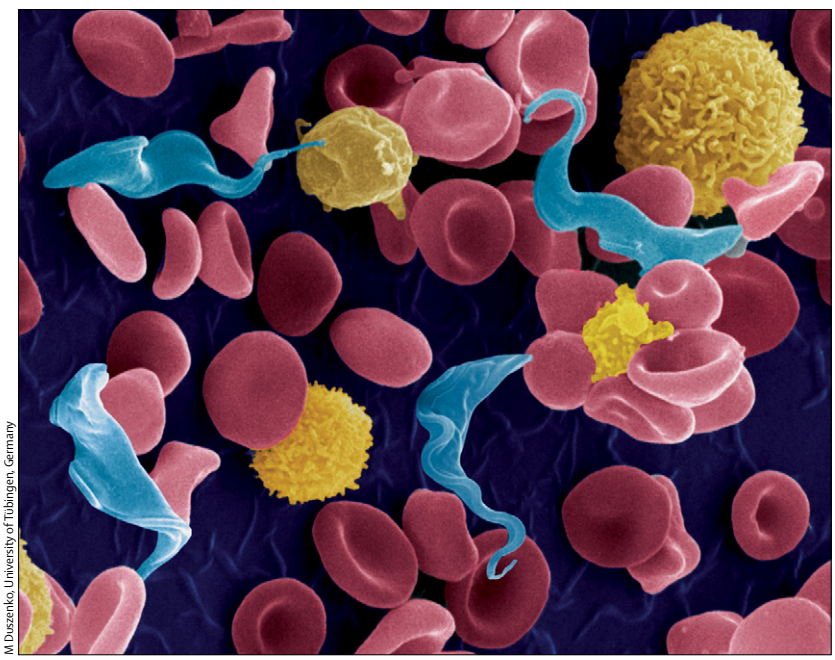


Figure 3: **Life cycle of African trypanosomes**
In man the bloodstream forms show a polymorphism with (A) dividing (black arrows) slender forms, (B) intermediate forms, and (C) stumpy forms. In the tsetse fly vector, bloodstream forms transform to (D) dividing midgut forms, then to (E) the migrating epimastigote forms, which develop in the salivary glands to (F) the infective metacyclic forms, which are injected during the next blood meal into the mammalian host. Reproduced from Vickerman K. Developmental cycles and biology of pathogenic trypanosomes. *Br Med Bull* 1985; **41:** 105–14, with permission of Oxford University Press.



M Duszenko, University of Tübingen, Germany

Figure 4: Trypanosomes among blood cells

F Chappuis

Figure 5: Screening for trypanosomiasis taking place under mango trees in Kajo-Keji county, Sudan

much slower progression into the second disease stage in the chronic form hampers direct comparison of the populations and further investigation of this topic will be needed.

Diagnosis

The diagnosis and staging of *T b gambiense* disease rely on laboratory examinations, because the clinical features of the disease are not sufficiently specific.[23,71,72] A three-step approach is used within control programmes and for individual patients: screening, diagnostic confirmation, and staging.

The card agglutination test for trypanosomiasis/*T b gambiense* (CATT), developed in the late 1970s, can be done on serum, capillary blood obtained from a finger prick, or blood from impregnated filter papers.[73–75] CATT is a fast and practical serological test that allows hundreds of individuals to be screened daily, and is reported to be 87–98% sensitive and 93–95% specific.[76–80] CATT is the best-adapted and most efficient screening method, and is widely used for mass population screening in endemic areas (figure 5).[81,82] However, since the test is used in populations where the prevalence of African trypanosomiasis is usually less than 5%, the positive predictive value of a positive CATT remains too low for confirmation of the disease. There are indications that CATT results might be misleading in specific areas as a result of the absence of the LiTat 1·3 antigene.[83] Other highly sensitive serological tests, such as immunofluorescence or enzyme-linked immunosorbent assays, are generally used in non-endemic countries to screen individuals with suggestive clinical features or previous exposure.[79,84] Since serological tests are not 100% sensitive, health professionals are advised to search for trypanosomes in individuals with negative serological tests who have had a recent infection (chancre) or a strong clinical suspicion of African trypanosomiasis.

The microscopic examination of lymph node aspirate and blood, or both, is needed for parasitological confirmation. The delay between sampling and examination should be kept as short as possible to avoid lysis of trypanosomes. When present, a cervical lymph node is punctured and the fresh aspirate swiftly examined. The sensitivity of lymph node palpation and aspiration varies from 40% to 80% dependent on parasite strain, stage of disease (this test is more sensitive during the first stage), and prevalence of other diseases that cause lymphadenopathy.[85,86] Because examination of thin or thick blood films has very low sensitivity, concentration methods such as the microhaematocrit centrifugation technique,[87] quantitative buffy coat,[88,89] and miniature anion-exchange centrifugation technique[90] should be used.[82,91,92] Serial examinations on consecutive days increase the sensitivity of blood examination techniques. Detection of parasite nucleic acids by PCR might become useful as a more sensitive approach, but existing tests need further standardisation and clinical validation.[71] Some investigators recommend treatment of individuals with high CATT titres (≥1:16), even if parasitological examination is negative, in populations with high disease prevalence (>1%), especially when the most sensitive blood detection methods (quantitative buffy coat or miniature anion-exchange centrifugation technique) cannot be used.[93,94] This strategy should not be applied when disease prevalence is low.[95]

Because treatment differs substantially between the first and second stage, differentiation between them by examination of the CSF after lumbar puncture is essential.[96] According to WHO recommendations[75] the presence in CSF of more than five white blood cells per µL, trypanosomes, or increased protein content (>370 mg/L) defines second-stage disease. The five cells per µL threshold is most widely used, but some controversy exists about the group of patients with six to

20 cells per µL, because this group is composed of individuals with or without signs of neuroinflammation and with various clinical responses to pentamidine, which is the drug used to treat first-stage disease.[97–100] Whereas the microscopic finding of trypanosomes is diagnostic of second-stage disease, the clinical significance of a positive PCR on a CSF sample is controversial.[101,102] Total protein measurement in the CSF is no longer recommended. By contrast, increased IgM concentrations in CSF, caused by synthesis within the spinal cord, are an early and specific marker of CNS invasion.[103–105] A field-designed latex agglutination test for IgM in CSF has shown promising results, but needs further validation.[106] Antibodies against neurofilaments, galactocerebrosides, neurofilaments, and glial fibrillary acidic proteins are also promising CSF markers of second-stage disease.[107–109]

The diagnostic approach for *T b rhodesiense* disease differs from that for *T b gambiense* in several ways. First, there is no serological screening test for *T b rhodesiense*. Rather, the identification of suspected cases relies on the non-specific clinical presentation and history of exposure. Second, parasitological confirmation is easier for *T b rhodesiense*, because the density of blood circulating parasites is higher than for *T b gambiense*. A thin or thick blood smear is usually sufficient to confirm diagnosis. And third, biological indices such as haemoglobin and platelet counts, and coagulation tests are more frequently or substantially changed in African trypanosomiasis caused by *T b rhodesiense* than in that caused by *T b gambiense*, but these findings remain non-specific.

Research and development of methods for diagnosis and staging of disease have been revitalised, notably through an initiative launched in 2006 by WHO and the Foundation for Innovative New Diagnostics (FIND).[110] Present research efforts focus on several areas: (i) recombinant or native trypanosome antigens that could be used to develop an improved serological test; (ii) methods to detect parasite antigens in blood or CSF; (iii) proteomic fingerprinting; (iv) low-tech PCR methods such as loop-mediated isothermal amplification or oligochromatography; and (v) new blood or CSF markers of second-stage disease.[111–115]

Treatment

Pentamidine

Few drugs are available to treat human African trypanosomiasis and selection is based mainly on the disease stage and causative pathogen (table). At present, all drugs are donated to WHO by the producers.[116,117]

Pentamidine is the drug of choice for treatment of first-stage disease caused by *T b gambiense*. It is given intramuscularly for a week , unless it can be given as an intravenous infusion in saline over 2 h. There is pharmacokinetic evidence that three injections might be equally effective,[118,119] and a comparative clinical trial is in progress to test this strategy (trial registration ISRCTN55042030). By contrast, the use of pentamidine in intermediate-stage disease (ie, up to ten or 20 white blood cells per µL in CSF)[120] has produced equivocal outcomes[97,99,100] and should not be generally recommended. Attention has been drawn to an unintended modification of the dose calculation from the base to the salt,[121] but this change should lead to a clarification of the label rather than a change in practice, because pentamidine at the currently used dose is still very effective. Pentamidine is generally well tolerated. When given by intramuscular injection, site pain and transient swelling, abdominal pain and gastrointestinal problems, and hypoglycaemia (5–40%) are the most frequently reported adverse events.[122] Other important adverse drug reactions such

For **FIND** see http://www.finddiagnostics.org

	Stage	Route of application	Dosing	Main adverse drug reactions
Trypanosoma brucei gambiense				
Pentamidine*	First	Intramuscular	4 mg/kg bodyweight at 24 h intervals for 7 days	Hypoglycaemia, injection site pain, diarrhoea, nausea, vomiting
Eflornithine	Second	Intravenous Infusion of >30 min	100 mg/kg bodyweight at 6 h intervals for 14 days	Diarrhoea, nausea, vomiting, convulsions; anaemia, leucopenia, and thrombocytopenia
Melarsoprol†	Second	Intravenous	2·2 mg/kg bodyweight at 24 h intervals for 10 days	Encephalopathic syndromes, skin reactions (pruritus, maculopapular eruptions), peripheral motoric (palsy) or sensorial (paraesthesia) neuropathies, thrombophlebitis
Trypanosoma brucei rhodesiense				
Suramin*	First	Intravenous	Test dose of 4–5 mg/kg bodyweight at day 1, then five injections of 20 mg/kg bodyweight every 7 days (eg, day 3, 10, 17, 24, 31); maximum dose per injection 1 g	Hypersensitivity reactions (acute, late); albuminuria, cylinduria, haematuria, peripheral neuropathy
Melarsoprol*	Second	Intravenous	Three series of 3·6, 3·6, 3·6 mg/kg bodyweight, the series spaced by intervals of 7 days; maximum dose per day 180 mg	Encephalopathic syndromes, skin reactions (pruritus, maculopapular eruptions), peripheral motoric (palsy) or sensorial (paraesthesia) neuropathies, thrombophlebitis

*Endemic countries: according to national legislature or guidelines. †Only where eflornithine is not available or where melarsoprol is first-line treatment according to national guidelines.

Table: **Standard treatments for human African trypanosomiasis and main adverse reactions**

as leucopenia, thrombocytopenia, hyperkalaemia, and QT-prolongation, which are seen in treatment of other diseases (eg, *Pneumocystis jirovecii* infection[123]), are rarely reported, probably because of the scarcity of adequate methods for patient monitoring.

Suramin

Suramin is used for first-stage *T b rhodesiense* disease, but is generally avoided against *T b gambiense* disease in western and central Africa because where *Onchocerca* spp are also present, its high activity against these parasites can expose patients to the risk of severe allergic reactions. The recommended dose regimens for suramin are complex and last up to 30 days.[124] The compound deteriorates rapidly in air and should be injected immediately after dilution in distilled water.[125] Adverse drug reactions are frequent but usually mild and reversible, including nephrotoxicity, peripheral neuropathy, and bone marrow toxicity with agranulocytosis and thrombocytopenia. Rare acute and late hypersensitivity reactions can occur,[32] of which the acute reaction is the reason for the low test dose generally applied before treatment initiation.

Melarsoprol

The organoarsenic compound melarsoprol remains the most widely used drug for treatment of second-stage disease caused by *T b gambiense* in resource-poor countries where the new drug eflornithine is not available or affordable, and it is the only choice for second-stage *T b rhodesiense*. For *T b gambiense* an abridged treatment schedule of ten injections on consecutive days was recommended by the International Scientific Council for Trypanosomiasis Research and Control.[126] For treatment of *T b rhodesiense*, various lengthy and complex treatment schedules are still used (table); work on the abridged schedule is continuing. Adverse reactions to melarsoprol are frequent and can be severe or even life-threatening. The most important reaction is an encephalopathic syndrome, which occurs with very variable frequency in an average 4·7% of *T b gambiense* and 8·0% of *T b rhodesiense* patients, with a case fatality rate of 44% and 57%, respectively.[127] For the management of encephalopathic syndrome, dexamethasone and diazepam are recommended.[122] Careful monitoring of the patient during treatment is crucial and although not indicative, the appearance of fever or fever combined with headaches can be regarded as warning signs.[128]

Skin reactions such as pruritus and maculopapular eruptions are fairly common, but severe complications such as bullous eruptions occur in less than 1% of cases.[78,126] Peripheral motor (palsy) or sensorial (paraesthesia) neuropathies have been reported. A good injection technique is mandatory to mitigate the irritating and painful effects of the injections, often leading to thrombophlebitis. In several foci, treatment failures have reached 30% of those treated. These failures suggest the emergence of resistance to melarsoprol, in which a P2 adenosine transporter might be implicated.[129] So far, however, difficulties in retrieval of *T b gambiense* isolates from patients have hampered demonstration of parasite resistance.

Eflornithine

Eflornithine is the only new molecule for the treatment of human African trypanosomiasis that has been registered in the past 50 years. Several studies comparing melarsoprol with eflornithine have shown a clearly reduced mortality with eflornithine, which is therefore recommended as the first-line treatment for second-stage *T b gambiense* disease,[130–132] but the use of eflornithine against *T b rhodesiense* is not advised, because this organism is innately less susceptible to the drug than is *T b gambiense*.[133] Treatment of *T b gambiense* infection with eflornithine lasts for 2 weeks, and because of the short half-life of the drug, four short infusions per day are necessary (see table). This regimen hampers the replacement of melarsoprol by eflornithine in rural public treatment facilities. The provision of kits by WHO, including all the necessary ancillary materials, could mitigate some of the difficulties.[134] Attempts were made to reduce the difficulty of drug administration by use of an oral formulation, but were abandoned after a pharmacokinetic trial gave discouraging results.[135,136] Adverse drug reactions are similar to those of other cytostatic drugs, and include bone marrow toxicity leading to anaemia, leucopenia, and thrombocytopenia (25–50%), gastrointestinal symptoms (10–39%), and convulsions (7%).[137] Superimposed bacterial infection at the catheter site can lead to life-threatening sepsis, but this event can be prevented by adequate nursing care.[138]

Prevention and control

There is no vaccine against trypanosome infection, and chemoprophylaxis is not recommended because of the toxicity of the drugs and the low risk of infection. The only preventive measure is reduction of tsetse fly bites. The flies are attracted to dark colours, in particular blue and black, and to the motion of vehicles. They can bite through thin clothes, and insect repellents provide only part protection. Travellers can take some preventive measures, such as avoidance of areas where tsetse flies are known to be present, travelling in cars with screened or closed windows in endemic foci, use of insect repellents, and clothes of wrist and ankle length. After a person is bitten by a tsetse fly, they should be monitored, although the risk of an infection is low. If a chancre, fever, or other symptom develops, an aspirate of the chancre, the blood, and possibly a lymph node aspirate should be examined for the presence of trypanosomes. In *T b gambiense* areas the CATT could be used.

The most important control measure for *T b gambiense* disease is active case-finding followed by treatment of the identified patients. Infected people can remain

asymptomatic for long periods before they develop signs of sleeping sickness, but they always act as a reservoir. Although animals have a less important role as reservoirs for *T b gambiense*, for *T b rhodesiense*, domestic (cattle, dogs) and wild animals (mainly antelopes) provide a vast reservoir that should be taken into consideration for control.[139,140] Vector control by use of tsetse fly traps or screens, in combination with odours that attract the flies, or insecticides, helps to reduce the fly density. Chemoprophylaxis is no longer in use because of the poor risk-benefit ratio caused by the adverse effects of the drugs.

The biological cycle of human African trypanosomiasis is very fragile because transmission through the tsetse fly is complex and slow. As a result, even in countries where the disease is endemic, less than 0·1% of flies carry mature parasites. The prevalence in man is also low apart from in epidemic foci. If the density of flies and infected individuals is lower than crucial limits, transmission can break down. This situation is more likely to occur for disease due to *T b gambiense* (small animal reservoir) than for that caused by *T b rhodesiense* (substantial reservoir of domestic and wild animals).

In 2002, the WHO HAT [human African trypanosomiasis] control and surveillance programme established a worldwide alliance to eliminate sleeping sickness.[141] Even earlier, the Pan-African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) was founded as a taskforce uniting African countries affected by African trypanosomiasis to fight and eventually eliminate the disease.[142] The main strategy of PATTEC is elimination of the tsetse fly in isolated foci through an integrated approach that combines insecticide spraying, traps, and the sterile insect technique. The use of sterile male flies resulted in the eradication of tsetse flies on Unguja Island in Zanzibar,[143] but the enormous cost of this method is likely to restrict its use, especially in areas where several vector species cause transmission. Many tsetse control experts do not share the PATTEC view, but rather advocate the use of simple technologies such as traps in combination with insecticides and attractants.[144] For the region endemic for *T b rhodesiense* a restricted application of insecticides to cattle (especially belly and legs) represents a cost-effective method of tsetse control.[145]

Elimination of African trypanosomiasis is thought to be feasible by WHO.[15] However, a prerequisite is to have new reliable methods for diagnosis and staging, and new, safe, effective, and easy-to-apply drugs for both stages of disease. Furthermore, participation of the national programmes of all affected African countries is paramount. To guarantee sustainability, additional partners are needed—international organisations, non-governmental organisations, and philanthropic organisations—to maintain the effort over decades. If this strategy can be realised, efforts to eliminate the disease will have a real chance of success.

Research priorities

Recent efforts have focused on finding optimum therapeutic regimens and on development of combination therapy with drugs already registered or those used to treat related diseases. For example, the oral drug nifurtimox, registered for treatment of Chagas disease, was considered for compassionate treatment, in combination with other trypanocidal drugs, of patients who did not respond to melarsoprol.[146] Gastrointestinal disturbances with nausea, abdominal pains, and vomiting are very frequent, and neurological adverse reactions with general convulsions, tremor, or agitation can occur.[32] The frequency of adverse reactions increases with treatment duration and all are rapidly reversible after discontinuation of the drug.[147]

Various combinations of eflornithine, melarsoprol, and nifurtimox have been tested and in all trials the efficacy was better than with monotherapy. However, combinations containing melarsoprol resulted in very high rates of severe adverse drug reactions.[146,148] As a result of those investigations, a multicountry trial of nifurtimox-eflornithine combination therapy was undertaken to compare the standard eflornithine therapy with an abridged regimen consisting of 200 mg/kg of eflornithine given as a short intravenous infusion every 12 h for 7 days, combined with nifurtimox 5 mg/kg given orally every 8 h for 10 days. This regimen reduces the number of infusions from 56 to 14 and the treatment duration from 14 to 10 days.[149,150] Some data reported so far suggest the combination is rather well tolerated and has a good intermediary effectiveness.[150]

The development of new medicines against human African trypanosomiasis underwent a serious setback when the new oral first-stage diamidine drug, pafuramidine maleate (DB289), failed almost at the end of the development programme because of nephrotoxicity.[151,152] However, a back-up programme identified new diamidines that could cure a CNS mouse model of infection (JE Hall and R Brun, unpublished results). Currently, no molecules are at the stage of clinical development for treatment of African trypanosomiasis. However, one molecule, the nitroimidazole fexinidazole, has been advanced from discovery to the preclinical stage, and profiling is in progress. If this process is successful, the first phase 1 studies in man should begin in 2009.[153,154]

Contributors

RB designed the article and drafted the sections on parasite and vector, and control. JB and FC drafted the clinical and diagnostic sections and contributed illustrations to the epidemiology. CB drafted the section on treatment and was responsible for an in-depth review of published work. All authors were involved in the finalisation of the manuscript and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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