Eur J Clin Microbiol Infect Dis (2012) 31:905–913
DOI 10.1007/s10096-011-1403-y

REVIEW

Human African trypanosomiasis in endemic populations and travellers

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Received: 12 August 2011 / Accepted: 22 August 2011 / Published online: 7 September 2011

Abstract Human African trypanosomiasis (HAT) or sleeping sickness is caused by the protozoan parasites *Trypanosoma brucei (T.b.) gambiense* (West African form) and *T.b. rhodesiense* (East African form) that are transmitted by the bite of the tsetse fly, *Glossina spp.*. Whereas most patients in endemic populations are infected with *T.b. gambiense*, most tourists are infected with *T.b. rhodesiense.* In endemic populations, *T.b. gambiense* HAT is characterized by chronic and intermittent fever, headache, pruritus, and lymphadenopathy in the first stage and by sleep disturbances and neuropsychiatric disorders in the second stage. Recent descriptions of the clinical presentation of *T.b. rhodesiense* in endemic populations show a high variability in different foci. The symptomatology of travellers is markedly different from the usual textbook descriptions of African HAT patients. The onset of both infections is almost invariably an acute and febrile disease. Diagnosis and treatment are difficult and rely mostly on old methods and drugs. However, new molecular diagnostic technologies are under development. A promising new drug combination is currently evaluated in a phase 3 b study and further new drugs are under evaluation.

Introduction

Human African trypanosomiasis (HAT) or sleeping sickness is caused by the protozoan parasites *Trypanosoma brucei (T.b.) gambiense* and *T.b. rhodesiense* that are transmitted by the bite of the tsetse fly (*Glossina spp.*). The disease presents in two stages: the first (early or haemato-lymphatic) stage and the second (late or meningo-encephalitic) stage.

Epidemiology

Endemic countries

In the last decade the number of reported HAT cases decreased from 37,385 (1998) to 9,589 (2009) per year with over 96% of cases caused by *T.b. gambiense*. The affected countries are shown in Fig. 1 [1, 2]. HAT is commonly transmitted in rural regions. Nevertheless, a recent description of HAT among urban residents of Kinshasa (Democratic Republic Congo [DRC]) shows that residents living in periurban belts can also be affected [3].

Non-endemic countries

HAT due to *T.b. gambiense* is rare among travellers, but was sporadically reported in immigrants and long-term Caucasian residents living in rural settings [4–6]. In contrast, *T.b. rhodesiense* HAT is frequently seen in short-term travellers to East African game reserves. The countries of infection of 83 travellers are shown in Fig. 1 [7–11].

Clinical presentation

The clinical presentation of HAT depends on the parasite species and on the host (Table 1).

Endemic countries

T.b. gambiense HAT

T.b. gambiense HAT is characterised by a chronic progressive course leading to death if untreated. According to

Electronic supplementary material The online version of this article (doi:10.1007/s10096-011-1403-y) contains supplementary material, which is available to authorized users.

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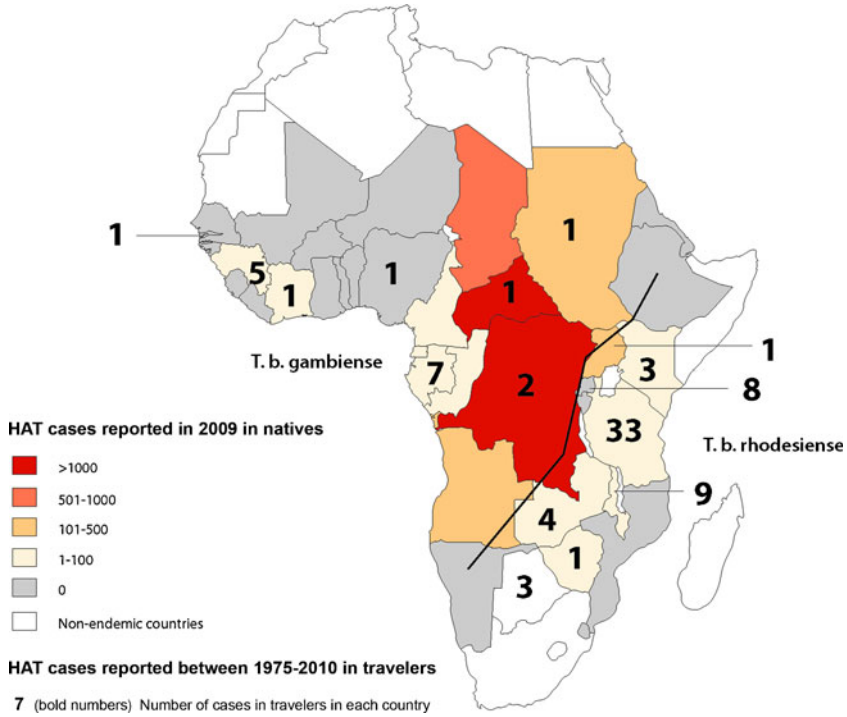

Fig. 1 Human African trypanosomiasis (HAT) in endemic and non-endemic populations (traveller) [8]. The black line divides the endemic regions of *T. b. gambiense* and *T.b. rhodesiense* HAT

models based on survival analysis the estimated duration of HAT is almost three years, evenly split between the first and the second stages [12]. A trypanosome chancre (local reaction at the bite site of the tsetse fly) is only exceptionally observed. Chronic and intermittent fever, headache, pruritus, lymphadenopathy and, to a lesser extent, hepato-splenomegaly are the leading signs and symptoms of the first stage. In the second stage sleep disturbances and neuro-psychiatric disorders dominate the clinical presentation and fever is rarely present [13, 14].

Sleep disorder is the leading symptom, hence the name "sleeping sickness". Somnographic studies have demonstrated 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" [15, 16]. The circadian rhythm of secretion of prolactin, renin, growth hormone, and cortisol levels disappears in severe cases [15].

The neurological symptoms include tremor, fasciculations, general motor weakness, paralysis of an extremity, hemiparesis, akinesia and abnormal movements such as dyskinesia or choreoathetosis, Parkinson-like movements, unspecific movement disorders, speech disorders, and abnormal archaic reflexes. These disorders are rarely seen during the first stage and increase with the duration of the disease [13, 17].

Cardiac involvement documented by ECG alterations is observed in over 50% of patients in first stage of *T.b. gambiense* HAT and increases to 70% in the second stage [18]. However, it rarely leads to relevant clinical heart failure [19, 20]. The most frequent ECG changes are QTc prolongation, repolarisation changes, and low voltage. This QTc prolongation comprises a risk of fatal arrhythmias, but relevant arrhythmias are only rarely—lacking respective facilities—documented in endemic countries [19]. Based on unpublished observations, there is a minority of patients who die suddenly without explanation. In these cases arrhythmias might be responsible for the fatal outcome [21]. Treatment with corticosteroids has been recommended to suppress inflammatory responses in the conduction system [21–24], but this has never been evaluated in a controlled trial. Endocrine disorders of the thyroid and adrenocortical function comprise hypo- and hyperfunction, but rarely demand specific treatment [25].

T.b. rhodesiense HAT

T.b. rhodesiense HAT is classically described as an acute disease progressing to second stage within a few weeks and death within 6 months [26]. The clinical presentation is similar, but trypanosomal chancres are more frequently seen (5–26%) [27–31], the localisation of enlarged lymph nodes is rather submandibular, axillary and inguinal than nuchal, and oedemas are more frequently observed [28, 32]. However, recent descriptions of the clinical presentation show a high variability in different foci [27, 33], possibly due to different strains [34]. Whereas fever and headache were the leading symptom in the first stage in some foci (96%) [31], tremor

Table 1 Signs and symptoms according to stage and affected population

Signs and symptoms	Population	*T.b. gambiense*		*T.b. rhodesiense*	
		First stage	Second stage	First stage	Second stage
Incubation period	Natives	18 months [12]	18 months [12]	1–3 weeks	Few weeks
	Travellers	75% <1 month	No data	<3 weeks	> 4 weeks
Chancre	Natives	<5% [95–97]	0% [13, 14]	5–26% [27–31]	0 [27, 33]
	Travellers	55.6%	33%	87.9%	75%
Trypanosomal rash	Natives	0% [95–97]	0% [13, 14]	0% [28, 29, 31]	0 [27, 33]
	Travellers	22.2%	50%	24.4%	41.7%
Fever (≥37.5°C)	Natives	10–20% [95–97]	10–40% [13, 14, 95–100]	28–90% [27, 31]	18–37% [27, 29, 30, 33]; 72% [28]
	Travellers	88.9%; >38.5°: 55.6%	100%; >38.5°: 50%	100%; >38.5°: 72.7%	91.7%; >38.5°: 50%
Lymphadenopathy	Natives	79–95% [95–97]	56–85% [13, 14, 95–97]	21% [27]	51–80% [27–30, 33]
	TraTravellersvelers	Generalized 33.3%	Generalized 50%	Generalized 6.1%	Generalized 33.3%
		Satellite (to chancre) 22.2%	Satellite (to chancre) 50%	Satellite (to chancre) 30.3%	Satellite (to chancre) 16.7%
Sleeping disorder	Natives	Somnolence 18%	Somnolence 29–41% [13, 14]	Somnolence 25–33% [27, 31]	Somnolence 54–66%
		Insomnia 73% [97]	Insomnia 25–57% [13, 14, 97]		Insomnia 28-64% [27–30, 33]
	Travellers	Somnolence 0%	Somnolence 0%	Somnolence 0%	Somnolence 16.7%
		Insomnia 28.6%	Insomnia 16.7%	Insomnia 6.7%	Insomnia 8.3%
Pruritus	Natives	29–33% [96, 97, 101]	17–57% [13, 14, 96, 97, 101]	0% [27]	6–53% [28, 30, 33]
	Travellers	22.2%	16.7%	3%	8.3%
Headache	Natives	51–80% [96, 101]	38–79% [13, 14, 96, 97, 101, 102]	96% [31]	51–80% [27, 33]
	Travellers	55.5%	50%	42.4%	66.7%
Hepatomegaly	Natives	0–20% [96, 97, 101]	7–17% [14, 97]	0–40% [27]	6–30% [27, 33]
	Travellers	22.2%	50%	15.6%	25%
Splenomegaly	Natives	9–27% [96, 97, 101]	5–19% [14, 96, 97]	0–36% [27]	16–58% [27, 33]
	Travellers	55.6%	66.7%	30.3%	8.3%
Tremor	Natives	5% [95]	19–21% [14, 75]	17–61% [27]	16–67% [27, 33]
	Travellers	14.3%	0%	0%	16.7%
Neurological disorder	Natives	<20% [96, 97]	20–40% [13, 97]	<20% [27]	50–58% [27, 33]
	Travellers	25%	33.3%	0%	8.3%
Psychiatric disorders	Natives	<10%	25% [13]	17% [29]	15–22% [27, 33]
	Travellers	0%	0%	3.3%	8.3%
Kidney impairment	Natives	Rare [66]	Rare [25, 66]	Unknown [27]	Unknown
	Travellers	0%	0%	85%	77.7%

(61%) and somnolence (58%) dominated in other foci [27]. In the second stage, fever has less frequently been observed in most studies (14-37%) [27, 29, 30, 33], and fever is only moderate, rarely (4–9%) exceeding 38.4°C [33]. Pruritus, sleeping disorders, reduced consciousness, or neurological signs and symptoms such as tremor, abnormal movements or walking disabilities may predominate in some foci. Compared to *T.b. gambiense* HAT, thyroid dysfunction, adrenal insufficiency and hypogonadism are more frequently found and myocarditis is more severe and may even be fatal [35–37]. Liver involvement with hepatomegaly is usually moderate, but jaundice, hyperbilirubinaemia, and ascites have been observed [38].

The cause of the diversity of clinical presentations in different foci is still unclear. Host genetics, previous infections with apathogenic trypanosome species [39, 40], co-infections or a diversity of the parasite are discussed as possible factors. Different parasite genotypes causing different clinical pic-

tures were confirmed for trypanosome isolates on the basis of the SRA (serum resistance associated) gene polymorphisms [34]. A co-infection with HIV or malaria does not influence the clinical presentation of HAT [33].

Non-endemic countries

The symptomatology of Europeans is markedly different from the usual textbook descriptions of African HAT patients. The onset of the diseases is almost invariably acute and of the febrile type, regardless of the involved species [8, 41].

T.b. rhodesiense HAT has a short incubation period of a few days in travellers (less than 3 weeks). It is an acute, life-threatening disease with the cardinal symptoms of high fever, headache, and a trypanosomal chancre [7, 10, 11, 42–47]. For *T.b. gambiense* HAT the incubation period in travellers is often shorter than 1 month, but might be as long as 7 years in immigrants (Thomas Zoller, personal communication, 2008).

Fever is nearly always present in both species and exceeds 38.5°C in more than 50% of cases [8]. If left untreated, the pyrexial episodes become irregular. Each attack may last from a day to a week and attacks may be separated by a few days to month-long intervals [41]. A trypanosomal chancre consists of a tender, purplish, indurated area which develops at the site of the tsetse fly bite. The lesion develops within 5–15 days, may ulcerate, and is often accompanied by a satellite lymphadenopathy. Within a few weeks, the chancre disappears without leaving a mark [41]. It is seen in about 84% of *T.b. rhodesiense* and 47% of *T.b. gambiense* HAT patients. A trypanosomal rash may appear in 25–35% of cases at any time after the first febrile episode, consisting of non-itching, blotchy, irregular erythematous macules with a diameter of up to 10 cm. A large proportion of the macules develop a central area of normal coloured skin, giving the rash a circinate or serpiginous outline. The rash is evanescent, fading in one place and reappearing in another over a period of several weeks [6, 41].

The classical sleep disorders and neurological findings of HAT are not a hallmark in travellers, irrespective of species. Sleep disorders were only present in a minority of cases in the *T.b. rhodesiense* and night time insomnia in 21% of *T.b. gambiense* HAT. Apart from tremors and motor deficits observed in 15% of *T.b. gambiense* infected travellers, neurological and psychiatric findings were absent. Since most of the travellers were in the first stage and had a short duration of the disease, sleep disorders and neuropsychiatric findings may not have developed at the time of the first clinical assessment.

Headache, lymphadenopathy, hepatomegaly, and splenomegaly are unspecific findings seen in about a quarter to half of the patients in both species. Unspecific gastrointestinal symptoms such as nausea, vomiting and diarrhoea are more prevalent in *T.b. rhodesiense* patients. Interestingly, jaundice has been reported in 28% of *T.b. rhodesiense* infections. ECG alterations due to myopericarditis [48] and conduction abnormalities such as transient second- and third-degree atrioventricular block [49], supraventricular tachycardia, and ventricular premature captures [50] have been reported. In a few travellers HAT has been complicated by renal failure requiring haemodialysis [47], multiorgan failure [44, 46], disseminated intravascular coagulopathy [46], and coma with even fatal outcome [7, 9].

The clinical presentation of HAT in immigrants is dominated by low grade fever and neuropsychiatric disorders. Due to predominant psychiatric symptoms some HAT patients have even been admitted to psychiatric clinics [8]. Because of the long incubation period, HAT has to be considered even if the patient has left the endemic country years ago.

Diagnosis

Endemic countries

The diagnosis is based on the visualisation of the parasite in lymph node aspirate, peripheral blood or cerebrospinal fluid (CSF), PCR technology and serologic testing.

Parasite numbers in the peripheral blood of patients with *T.b. gambiense* HAT vary between more than 10,000 trypanosomes/ml to less than 100 trypanosomes/ml, which is below the detection limit of microscopic examination of wet blood films, Giemsa stained thin blood films or thick blood films (5,000–10,000 trypanosomes/ml) [51]. The sensitivity can be improved by using more sophisticated concentration methods such as microhaematocrit centrifugation techniques or quantitative buffy coat (detection limit: 450–500 trypanosomes/ml) or the mini-anion-exchange centrifugation technique (50–100 trypanosomes/ml) or a combination of both techniques (10 trypanosomes/ml) [52]. In contrast, the parasitaemia is more constant and higher in *T.b. rhodesiense* patients and the visualisation of the parasite in the blood smear poses less problems. The sensitivity of parasitological examination of lymph node aspirate varies between 40% and 80% [51].

The Card Agglutination Test for trypanosomiasis (CATT) is a cost-efficient screening method for mass screening of *T. b. gambiense* HAT. In most endemic regions its sensitivity varies from 87% to 98%. However, the CATT test is not sensitive for *T.b. rhodesiense* [51].

Although a wide range of sensitive molecular tests for the diagnosis of HAT are described in more than 20 publications, none of these tests has been fully evaluated. Only recently PCR was evaluated in a large scale trial in

DRC for diagnosis, staging, and follow up. The performance of PCR to diagnose sleeping sickness (sensitivity 88%, specificity 99%), and to detect CNS involvement (sensitivity 88%, specificity 83%) was better or similar to current diagnostic techniques, but PCR was unreliable for monitoring treatment outcome. Positive PCR results in otherwise normal CSF have to be interpreted with caution. Besides blood contamination during lumbar puncture, dead parasites can explain positive PCR findings in the absence of CNS infection [53].

As treatment differs markedly between first and second stage HAT, staging of the disease by examination of CSF is essential. The definition of second stage HAT by an elevated white blood cell count (WBC >5/mm^3) or the presence of trypanosomes [54] in the CSF has limited sensitivity and may lead to wrong staging. New markers such as intrathecal immunoglobulin M, interleukin 10, markers of brain damage (CXCL10, CXCL8, lipocalin 2) or panels of such markers show promising results [55–59], but are neither yet completely validated nor commercially available.

With increasing rates of drug resistance the diagnosis of relapse becomes crucial. Control investigations of the CSF are recommended by the WHO 3, 6, 12, 18, and 24 months after treatment [54]. However, different criteria defining a relapse according to WBC count in the CSF have been published and there is no consensus on the definition of a relapse [60]. An algorithm with CSF analysis at 6 and 12 months showed a sensitivity of 94% and a specificity of 98% for detection of relapses. Patients with a WBC≤5 cells/μl without trypanosomes in CSF at 6 months had a low risk of treatment failure and did not need further tests. Patients with≥50 cells/μl and/or trypanosomes in the CSF were considered as treatment failure. The group of 6–49 cells/μl and no trypanosomes in CSF needed further follow-up investigations [61]. Latex IgM trypanosome specific antibodies in the CSF were a less accurate indicator of relapse than WBC count [61].

Non-endemic countries

Some practical issues are crucial for the correct diagnosis. A delay between sampling and examination can lead to a false negative result since trypanosomes do not survive a long time after the blood sample is taken. Additionally, the sample should be sent to the laboratory at a temperature of 2–8° (not frozen), be protected from sunlight, and tested within 12 hours [51]. The recognition of the parasite, mainly in thick blood smears and lymph node aspirates, requires experienced laboratory technicians. Microhaematocrit centrifugation techniques, quantitative buffy coat, or the mini-anion-exchange centrifugation technique are available only in specialised laboratories. Molecular techniques have some potential in travel clinics but are not yet implemented in routine diagnostics [62, 63]. Serological tests are not validated in travellers, their sensitivity varies from region to region [64] and their specificity can be as low as 61% [65].

Laboratory findings

Among *T.b. gambiense* HAT patients in endemic regions, anaemia and impaired renal function are frequent [19, 25], but liver enzymes, lactate dehydrogenase, creatinine kinase, and blood sugar are mostly normal [66]. In tourists with *T.b. rhodesiense* HAT, elevated creatinine (81%), liver enzymes (82%), low platelets (92%), and elevated levels of C reactive protein are frequent. Severe haematological disorders and elevated liver and kidney function tests have been reported [10, 11, 44, 47].

Radiological findings

The knowledge on magnetic resonance imaging (MRI) alterations in HAT patients is limited to a few case reports. The alterations are multifarious and include symmetrical focal lesions [67], diffuse hyperintensity [68], brain oedema with demyelination, brain atrophy, and multiple abnormal signals [69–71]. The alterations are localized in the brainstem, basal ganglia, white matter, and central gray matter. These lesions resolved after treatment [70].

Treatment

Endemic countries

The choice of the drug is directed by the species and the stage of the disease (Table 2). Recently, the recommended dose calculation for pentamidine has shifted from the base to the salt moiety, resulting in a significant reduction of the active molecule [72]. Whereas the dosage has been adapted in the treatment of cutaneous leishmaniasis [73], the dosage recommendations for HAT did not change and the efficacy continues to be excellent [74].

The main disadvantages of melarsoprol are the toxicity, including an encephalopathic syndrome (ES) comprising convulsions, progressive coma, and psychotic reactions [75], the long duration of treatment, and the increasing rate of treatment failures reaching up to 30% [74, 76, 77]. ES occurs variably with an average frequency of 4.7% for *T.b. gambiense* and 8% for *T.b. rhodesiense* HAT and has a fatality rate of about 50% [78]. In the absence of controlled trials there are currently no treatment guidelines of ES. However, dexamethasone 0.5–0.6 mg/kg/day divided in 4–6 doses against cerebral oedema, anticonvulsive treatment

Table 2 Treatment of human African trypanosomiasis (HAT) according to stage and species

Stage	*T.b. gambiense*	*T.b. rhodesiense*
First stage	Pentamidine	Suramin
	4 mg/kg i.m. at 24 hourly intervals for 7 days i.m. (or as i.v. short infusion)	Test dose of 200 mg i.v.
		20 mg/kg day 1, 3, 7, 14 and 21 [10]
Second stage	Eflornithine	Melarsoprol
	Intravenous eflornithine (100 mg/kg every 6 h) for 14 days	2.2 mg/kg i.v 10 daily doses
	Eflornithine/Nifurtimox combination	Pre-treatment with suramin
	Intravenous eflornithine (200 mg/kg every 12 h) for 7 days and oral nifurtimox (15 mg/kg per day, every 8 h) for 10 days	Test dose of 4–5 mg kg^{-1} body weight at day 1
	Melarsoprol	
	2.2 mg/kg i.v 10 daily doses	

in the presence of convulsions, correction of electrolyte dysbalance, and vasoactive substances to control arterial hypotension are recommended [78]. The prophylactic use of prednisone reduces incidence and mortality of the syndrome [79, 80]. A short-course melarsoprol treatment (daily injections of 2.2 mg/kg for 10 days) is established for *T.b. gambiense* HAT [81–84], and recent results showed non-inferiority to the previous treatment schedules for *T.b. rhodesiense* HAT. In second stage *T.b. rhodesiense* HAT, pre-treatment with suramin is proposed in some national guidelines to reduce parasitaemia before the initiation of melarsoprol.

Eflornithine monotherapy clearly reduced the mortality (1.2%) in comparison to melarsoprol (4.2–4.9%) and was more effective (one year survival probability 80–97% versus 71–92%) in second stage *T.b. gambiense* HAT [76, 85]. At present, the use of eflornithine against *T.b. rhodesiense* is not advised because of a lower susceptibility [86]. Adverse events include bone marrow toxicity leading to anaemia (9–21%), neutropenia (33–57%) and thrombocytopenia (4%), gastrointestinal symptoms with nausea, vomiting, and diarrhoea (10–39%), and convulsions (5–13%) [87–89]. The main problems of eflornithine are the short half life of the drug and the increasing rate of resistance to monotherapy (up to 14–30% in Angola, DRC, and Sudan [personal communication P. Simarro, WHO]). The treatment is administered over 14 days with four daily short infusions. However, the broad use in the field is limited, since the enormous weight of the infusion material (45 kg for one patient) causes major logistic problems. The total dosage of eflornithine can be reduced by half in the combination with nifurtimox (Nifurtimox Eflornithine Combination Treatment [NECT]), leading to increased cure rates (eflornithine monotreatment 92%; NECT 97–98%). While haematotoxic effects were reduced by half, nausea and vomiting increased to 50% [90]. Preliminary results of a phase 3b field study on NECT in remote rural settings show a similar pattern of adverse events and a fatality rate of only 1.6% [91].

A comparison of the encephalopathic syndrome between melarsoprol and eflornithine is difficult, since the definition of this syndrome [75, 79, 92–94] has not been adopted in the eflornithine trials. Whereas alterations of the level of consciousness (i.e. coma) appear more frequently with melarsoprol (4–5%) than with eflornithine (1–2%), convulsions are less frequently observed with melarsoprol (2–5%) than with eflornithine/NECT (5–13%) [75, 82–84, 88–90].

Since resistance cases against NECT were already observed, new drugs are desperately needed.

The most advanced new drug in the pipeline is fexinidazole which belongs to the nitroimidazole class. The substance proved to be orally active against *T.b. gambiense* and *T.b. rhodesiense* in animal studies and had an excellent safety profile. Since it penetrates the blood brain barrier it might be effective in both stages of sleeping sickness [74].

Non-endemic countries

Due to the paucity of HAT outside Africa, treatment recommendations are based on studies conducted in endemic regions. However, the intravenous application of pentamidine is preferred in travellers because of the risk for rhabdomyolysis observed with intramuscular administration [73]. Unfortunately, the limited availability of the drugs outside endemic regions and time pressure often determine the choice of drug. Thus, in some patients with first stage *T.b. rhodesiense* HAT, treatment was initiated with the more easily available pentamidine switching to suramine as soon as it became available [44]. This approach was successful. Since lethal outcome has been observed in

travellers, rapid diagnostic and initiation of treatment are necessary [8, 9].

References

1. WHO (2006) Human African trypanosomiais (sleeping sickness): epidemiological update. Weekly Epidemiological Record 8:71–80. WHO, Geneva
2. Simarro PP, Jannin J, Cattand P (2008) Eliminating human African trypanosomiasis: where do we stand and what comes next? PLoS Med 5:e55
3. Robays J, Ebeja Kadima A, Lutumba P, Miaka mia Bilenge C, Kande Betu Ku Mesu V, De Deken R, Makabuza J, Deguerry M, Van der Stuyft P, Boelaert M (2004) Human African trypanosomiasis amongst urban residents in Kinshasa: a case-control study. Trop Med Int Health 9:869–875
4. Bisoffi Z, Beltrame A, Monteiro G, Arzese A, Marocco S, Rorato G, Anselmi M, Viale P (2005) African trypanosomiasis gambiense, Italy. Emerg Infect Dis 11:1745–1747
5. Iborra C, Danis M, Bricaire F, Caumes E (1999) A traveler returning from Central Africa with fever and a skin lesion. Clin Infect Dis 28:679–680
6. Ezzedine K, Darie H, Le Bras M, Malvy D (2007) Skin features accompanying imported human African trypanosomiasis: hemolymphatic Trypanosoma gambiense infection among two French expatriates with dermatologic manifestations. J Travel Med 14:192–196
7. Jelinek T, Bisoffi Z, Bonazzi L, van Thiel P, Bronner U, de Frey A, Gundersen SG, McWhinney P, Ripamonti D (2002) Cluster of African trypanosomiasis in travelers to Tanzanian national parks. Emerg Infect Dis 8:634–635
8. Urech K, Neumayr A, Blum J (2011) Sleeping sickness in travelers; do they really sleep? PLoS Negl Trop Dis
9. Mendonca MM, Rasica M, van Thiel PP, Richter C, Kager PA, Wismans PJ (2002) Three patients with African sleeping sickness following a visit to Tanzania. Ned Tijdschr Geneeskd 146:2552–2556
10. Moore AC, Ryan ET, Waldron MA (2002) Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20–2002. A 37-year-old man with fever, hepatosplenomegaly, and a cutaneous foot lesion after a trip to Africa. N Engl J Med 346:2069–2076
11. Moore DA, Edwards M, Escombe R, Agranoff D, Bailey JW, Squire SB, Chiodini PL (2002) African trypanosomiasis in travelers returning to the United Kingdom. Emerg Infect Dis 8:74–76
12. Checchi F, Filipe JA, Haydon DT, Chandramohan D, Chappuis F (2008) Estimates of the duration of the early and late stage of gambiense sleeping sickness. BMC Infect Dis 8:16
13. Blum J, Schmid C, Burri C (2006) Clinical aspects of 2541 patients with second stage human African trypanosomiasis. Acta Trop 97:55–64
14. Blum J, Burri C (2002) Treatment of late stage sleeping sickness caused by *T.b. gambiense*: a new approach to the use of an old drug. Swiss Med Wkly 132:51–56
15. Buguet A, Bourdon L, Bisser S, Chapotot F, Radomski MW, Dumas M (2001) Sleeping sickness: major disorders of circadian rhythm. Med Trop (Mars) 61:328–339
16. Lundkvist GB, Kristensson K, Bentivoglio M (2004) Why trypanosomes cause sleeping sickness. Physiology (Bethesda) 19:198–206
17. Kennedy PG (2006) Human African trypanosomiasis—neurological aspects. J Neurol 253:411–416
18. Blum JA, Schmid C, Burri C, Hatz C, Olson C, Fungula B, Kazumba L, Mangoni P, Mbo F, Deo K, Mpanya A, Dala A, Franco JR, Pohlig G, Zellweger MJ (2009) Cardiac alterations in human African trypanosomiasis (*T.b. gambiense*) with respect to the disease stage and antiparasitic treatment. PLoS Negl Trop Dis 3:e383
19. Blum JA, Burri C, Hatz C, Kazumba L, Mangoni P, Zellweger MJ (2007) Sleeping hearts: the role of the heart in sleeping sickness (human African trypanosomiasis). Trop Med Int Health 12:1422–1432
20. Blum JA, Zellweger MJ, Burri C, Hatz C (2008) Cardiac involvement in African and American trypanosomiasis. Lancet Infect Dis 8:631–641
21. Collomb H, Bartoli D (1967) The heart in human African trypanosomiasis caused by *Trypanosoma gambiense*. Bull Soc Pathol Exot Filiales 60:142–156
22. Poltera AA, Cox JN, Owor R (1976) Pancarditis affecting the conducting system and all valves in human African trypanosomiasis. Br Heart J 38:827–837
23. Poltera AA, Hochmann A, Lambert PH (1980) A model for cardiopathy induced by Trypanosoma brucei brucei in mice. A histologic and immunopathologic study. Am J Pathol 99:325–351
24. Bertrand E, Serie F, Rive J, Compaore P, Sentilhes L, Baudin L, Renambot J, Chauvet J, Ekra A, Assamoi MO (1974) Current aspects of the cardiac symptoms in African human trypanosomiasis due to *Trypanosoma gambiense* (apropos of 194 cases). Acta Cardiol 29:363–381
25. Blum JA, Schmid C, Hatz C, Kazumba L, Mangoni P, Rutishauser J, la Torre A, Burri C (2007) Sleeping glands? The role of endocrine disorders in sleeping sickness (*T.b. gambiense* human African trypanosomiasis). Acta Trop 104:16–24
26. Odiit M, Kansiime F, Enyaru JC (1997) Duration of symptoms and case fatality of sleeping sickness caused by *Trypanosoma brucei rhodesiense* in Tororo, Uganda. East Afr Med J 74:792–795
27. MacLean LM, Odiit M, Chisi JE, Kennedy PG, Sternberg JM (2010) Focus-specific clinical profiles in human African trypanosomiasis caused by *Trypanosoma brucei rhodesiense*. PLoS Negl Trop Dis 4:e906
28. Boatin BA, Wyatt GB, Wurapa FK, Bulsara MK (1986) Use of symptoms and signs for diagnosis of *Trypanosoma brucei rhodesiense* trypanosomiasis by rural health personnel. Bull World Health Organ 64:389–395
29. Buyst H (1977) The epidemiology of sleeping sickness in the historical Luangwa valley. Ann Soc Belg Med Trop 57:349–359
30. Wellde BT, Chumo DA, Reardon MJ, Mwangi J, Asenti A, Mbwabi D, Abinya A, Wanyama L, Smith DH (1989) Presenting features of Rhodesian sleeping sickness patients in the Lambwe Valley, Kenya. Ann Trop Med Parasitol 83(Suppl 1):73–89
31. Mbulamberi DB (1987) A clinical analysis of 3151 cases of Rhodesian sleeping sickness treated in the South Eastern Uganda, during the year 1985. Proceedings of the International Scientific Council for Trypanosomiasis Research and Control 19th Meeting, Lomé, Togo, pp 188–195
32. Foulkes JR (1981) The six diseases WHO. Human trypanosomiasis in Africa. Br Med J (Clin Res Ed) 283:1172–1174
33. Kuepfer I, Hhary EP, Allan M, Edielu A, Burri C, Blum JA (2011) Clinical presentation of *T.b. rhodesiense* sleeping sickness in second stage patients from Tanzania and Uganda. PLoS Negl Trop Dis 5:e968
34. MacLean L, Chisi JE, Odiit M, Gibson WC, Ferris V, Picozzi K, Sternberg JM (2004) Severity of human african trypanosomiasis in East Africa is associated with geographic location, parasite genotype, and host inflammatory cytokine response profile. Infect Immun 72:7040–7044

35. Reincke M, Arlt W, Heppner C, Petzke F, Chrousos GP, Allolio B (1998) Neuroendocrine dysfunction in African trypanosomiasis. The role of cytokines. Ann NY Acad Sci 840:809–821
36. Jones IG, Lowenthal MN, Buyst H (1975) Electrocardiographic changes in African trypanosomiasis caused by *Trypanosoma brucei rhodesiense*. Trans R Soc Trop Med Hyg 69:388–395
37. Koten JW, De Raadt P (1969) Myocarditis in *Trypanosoma rhodesiense* infections. Trans R Soc Trop Med Hyg 63:485–489
38. Kouchner G, Bouree P, Lowenthal M (1979) Hepatic involvement in *Trypanosoma rhodesiense trypanosomiasis*. Bull Soc Pathol Exot Filiales 72:131–135
39. Blum J, Beck BR, Brun R, Hatz C (2005) Clinical and serologic responses to human 'apathogenic' trypanosomes. Trans R Soc Trop Med Hyg 99:795–797
40. Jamonneau V, Ravel S, Garcia A, Koffi M, Truc P, Laveissiere C, Herder S, Grebaut P, Cuny G, Solano P (2004) Characterization of *Trypanosoma brucei* s.l. infecting asymptomatic sleeping-sickness patients in Cote d'Ivoire: a new genetic group? Ann Trop Med Parasitol 98:329–337
41. Duggan AJ, Hutchinson MP (1966) Sleeping sickness in Europeans: a review of 109 cases. J Trop Med Hyg 69:124–131
42. Sinha A, Grace C, Alston WK, Westenfeld F, Maguire JH (1999) African trypanosomiasis in two travelers from the United States. Clin Infect Dis 29:840–844
43. Apted FJ, Smyly DP, Ormero WE, Stronach BW (1963) A comparative study of the epidemiology of endemic Rhodesian sleeping sickness in different parts of Africa. J Trop Med Hyg 66:1–16
44. Ripamonti D, Massari M, Arici C, Gabbi E, Farina C, Brini M, Capatti C, Suter F (2002) African sleeping sickness in tourists returning from Tanzania: the first 2 Italian cases from a small outbreak among European travelers. Clin Infect Dis 34:E18–E22
45. Braendli B, Dankwa E, Junghanss T (1990) East African sleeping sickness (*Trypanosoma rhodesi*ense infection) in 2 Swiss travelers to the tropics. Schweiz Med Wochenschr 120:1348–1352
46. Sanner BM, Doberauer C, Tepel M, Zidek W (2000) Fulminant disease simulating bacterial sepsis with disseminated intravascular coagulation after a trip to East Africa. Intensive Care Med 26:646–647
47. Oscherwitz SL (2003) East African trypanosomiasis. J Travel Med 10:141–143
48. Quinn TC, Hill CD (1983) African trypanosomiasis in an American hunter in East Africa. Arch Intern Med 143:1021–1023
49. Croft AM, Jackson CJ, Friend HM, Minton EJ (2006) African trypanosomiasis in a British soldier. J R Army Med Corps 152:156–160
50. Damian MS, Dorndorf W, Burkardt H, Singer I, Leinweber B, Schachenmayr W (1994) Polyneuritis and myositis in *Trypanosoma gambiense* infection. Dtsch Med Wochenschr 119:1690–1693
51. Chappuis F, Loutan L, Simarro P, Lejon V, Buscher P (2005) Options for field diagnosis of human african trypanosomiasis. Clin Microbiol Rev 18:133–146
52. Camara M, Camara O, Ilboudo H, Sakande H, Kabore J, N'Dri L, Jamonneau V, Bucheton B (2010) Sleeping sickness diagnosis: use of buffy coats improves the sensitivity of the mini anion exchange centrifugation test. Trop Med Int Health 15:796–799
53. Deborggraeve S, Lejon V, Ekangu RA, Mumba ND, Pati PP, Ilunga M, Mulunda JP, Buscher P (2011) Diagnostic accuracy of PCR in gambiense sleeping sickness diagnosis, staging and post-treatment follow-up: a 2-year longitudinal study. PLoS Negl Trop Dis 5:e972
54. WHO (1998) Control and surveillance of African trypanosomiasis. WHO Technical report, WHO, Geneva
55. Lejon V, Robays J, N'Siesi FX, Mumba D, Hoogstoel A, Bisser S, Reiber H, Boelaert M, Buscher P (2007) Treatment failure related to intrathecal immunoglobulin M (IgM) synthesis, cerebrospinal fluid IgM, and interleukin-10 in patients with hemolymphatic-stage sleeping sickness. Clin Vaccine Immunol 14:732–737
56. Lejon V, Buscher P (2005) Review article: cerebrospinal fluid in human African trypanosomiasis: a key to diagnosis, therapeutic decision and post-treatment follow-up. Trop Med Int Health 10:395–403
57. Kennedy PG (2010) Novel biomarkers for late-stage human African trypanosomiasis—the search goes on. Am J Trop Med Hyg 82:981–982
58. Hainard A, Tiberti N, Robin X, Lejon V, Ngoyi DM, Matovu E, Enyaru JC, Fouda C, Ndung'u JM, Lisacek F, Muller M, Turck N, Sanchez JC (2009) A combined CXCL10, CXCL8 and H-FABP panel for the staging of human African trypanosomiasis patients. PLoS Negl Trop Dis 3:e459
59. Amin DN, Ngoyi DM, Nhkwachi GM, Palomba M, Rottenberg M, Buscher P, Kristensson K, Masocha W (2010) Identification of stage biomarkers for human African trypanosomiasis. Am J Trop Med Hyg 82:983–990
60. Mumba ND, Lejon V, N'Siesi FX, Boelaert M, Buscher P (2009) Comparison of operational criteria for treatment outcome in gambiense human African trypanosomiasis. Trop Med Int Health 14:438–444
61. Mumba ND, Lejon V, Pyana P, Boelaert M, Ilunga M, Menten J, Mulunda JP, Van Nieuwenhove S, Muyembe Tamfum JJ, Buscher P (2010) How to shorten patient follow-up after treatment for *Trypanosoma brucei gambiense* sleeping sickness. J Infect Dis 201:453–463
62. Deborggraeve S, Buscher P (2010) Molecular diagnostics for sleeping sickness: what is the benefit for the patient? Lancet Infect Dis 10:433–439
63. Becker S, Franco JR, Simarro PP, Stich A, Abel PM, Steverding D (2004) Real-time PCR for detection of *Trypanosoma brucei* in human blood samples. Diagn Microbiol Infect Dis 50:193–199
64. Truc P, Lejon V, Magnus E, Jamonneau V, Nangouma A, Verloo D, Penchenier L, Buscher P (2002) Evaluation of the micro-CATT, CATT/Trypanosoma brucei gambiense, and LATEX/T b gambiense methods for serodiagnosis and surveillance of human African trypanosomiasis in West and Central Africa. Bull World Health Organ 80:882–886
65. Louis FJ, Buscher P, Lejon V (2001) Diagnosis of human African trypanosomiasis in 2001. Med Trop (Mars) 61:340–346
66. Bisser S, Bouteille B, Sarda J, Stanghellini A, Ricard D, Jauberteau MO, Marchan F, Dumas M, Breton JC (1997) Contribution of biochemical tests in the diagnosis of the nervous phase of human African trypanosomiasis. Bull Soc Pathol Exot 90:321–326
67. Sabbah P, Brosset C, Imbert P, Bonardel G, Jeandel P, Briant JF (1997) Human African trypanosomiasis: MRI. Neuroradiology 39:708–710
68. Gill DS, Chatha DS, Carpio-O'Donovan R (2003) MR imaging findings in African trypansomiasis. AJNR Am J Neuroradiol 24:1383–1385
69. Braakman HM, van de Molengraft FJ, Hubert WW, Boerman DH (2006) Lethal African trypanosomiasis in a traveler: MRI and neuropathology. Neurology 66:1094–1096
70. Serrano-Gonzalez C, Velilla I, Fortuno B, Guelbenzu S, Portoles A (1996) Neuroimaging and efficacy of treatment in advanced African trypanosomiasis. Rev Neurol 24:1554–1557
71. Bedat-Millet AL, Charpentier S, Monge-Strauss MF, Woimant F (2000) Psychiatric presentation of human African trypanosomiasis: overview of diagnostic pitfalls, interest of difluoromethylornithine treatment and contribution of magnetic resonance imaging. Rev Neurol (Paris) 156:505–509

72. Dorlo TP, Kager PA (2008) Pentamidine dosage: a base/salt confusion. PLoS Negl Trop Dis 2:e225
73. Blum JA, Hatz CF (2009) Treatment of cutaneous leishmaniasis in travelers. J Travel Med 16:123–131
74. Burri C (2010) Chemotherapy against human African trypanosomiasis: Is there a road to success? Parasitology 137:1987–1994
75. Blum J, Nkunku S, Burri C (2001) Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health 6:390–400
76. Balasegaram M, Young H, Chappuis F, Priotto G, Raguenaud ME, Checchi F (2009) Effectiveness of melarsoprol and eflornithine as first-line regimens for gambiense sleeping sickness in nine Medecins Sans Frontieres programmes. Trans R Soc Trop Med Hyg 103:280–290
77. Robays J, Nyamowala G, Sese C, Betu Ku MKV, Lutumba P, Van der V, Boelaert M (2008) High failure rates of melarsoprol for sleeping sickness, Democratic Republic of Congo. Emerg Infect Dis 14:966–967
78. Seixas J (2004) Investigations of the encephalopathic syndrome during melarsoprol treatment of human African trypanosomiasis. Dissertation, The Swiss Tropicla and Health Institute, Switzerland and the Universidade Nova de Lisboa, Portugal
79. Pepin J, Milord F, Khonde AN, Niyonsenga T, Loko L, Mpia B, De Wals P (1995) Risk factors for encephalopathy and mortality during melarsoprol treatment of *Trypanosoma brucei gambiense* sleeping sickness. Trans R Soc Trop Med Hyg 89:92–97
80. Pepin J, Tetreault L, Gervais C (1985) The use of oral corticosteroids in the treatment of human African trypanosomiasis: a retrospective survey in Nioki, Zaire. Ann Soc Belg Med Trop 65:17–29
81. Burri C, Nkunku S, Merolle A, Smith T, Blum J, Brun R (2000) Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense*: a randomised trial. Lancet 355:1419–1425
82. Schmid C, Richer M, Bilenge CM, Josenando T, Chappuis F, Manthelot CR, Nangouma A, Doua F, Asumu PN, Simarro PP, Burri C (2005) Effectiveness of a 10-day Melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (Impamel II). J Infect Dis 191:1922–1931
83. Pepin J, Mpia B (2006) Randomized controlled trial of three regimens of melarsoprol in the treatment of *Trypanosoma brucei gambiense* trypanosomiasis. Trans R Soc Trop Med Hyg 100:437–441
84. Burri C, Blum J, Brun R (1995) Alternative application of melarsoprol for treatment of *T.B. gambiense* sleeping sickness. Preliminary results. Ann Soc Belg Med Trop 75:65–71
85. Chappuis F, Udayraj N, Stietenroth K, Meussen A, Bovier PA (2005) Eflornithine is safer than melarsoprol for the treatment of second-stage *Trypanosoma brucei gambiense* human African trypanosomiasis. Clin Infect Dis 41:748–751
86. Iten M, Mett H, Evans A, Enyaru JC, Brun R, Kaminsky R (1997) Alterations in ornithine decarboxylase characteristics account for tolerance of *Trypanosoma brucei rhodesiense* to D, L-alpha-difluoromethylornithine. Antimicrob Agents Chemother 41:1922–1925
87. Burri C, Brun R (2003) Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res 90(Supp 1):S49–S52
88. Priotto G, Kasparian S, Ngouama D, Ghorashian S, Arnold U, Ghabri S, Karunakara U (2007) Nifurtimox-eflornithine combination therapy for second-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Congo. Clin Infect Dis 45:1435–1442
89. Priotto G, Pinoges L, Fursa IB, Burke B, Nicolay N, Grillet G, Hewison C, Balasegaram M (2008) Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. BMJ 336:705–708
90. Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, Ghabri S, Baudin E, Buard V, Kazadi-Kyanza S, Ilunga M, Mutangala W, Pohlig G, Schmid C, Karunakara U, Torreele E, Kande V (2009) Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet 374:56–64
91. Schmid C, Kande V, Mutombo W, Ilunga M, Lumpungu I, Mutanda S, Tete D, Nganzobo P, Mubwa N, Blum J, Balasegaram M, Valverde O (2010) NECT-FIELD: Clinical trial to evaluate the tolerability, feasibility, and effectiveness of NECT treatment in "real-life" conditions for late stage sleeping sickness. LB-2253, Annual Meeting, American Society of Tropiclal Medicine and Hygine, Poster Session C Presentations, 31-1-2010
92. Adams JH, Haller L, Boa FY, Doua F, Dago A, Konian K (1986) Human African trypanosomiasis (*T.b. gambiense*): a study of 16 fatal cases of sleeping sickness with some observations on acute reactive arsenical encephalopathy. Neuropathol Appl Neurobiol 12:81–94
93. Haller L, Adams H, Merouze F, Dago A (1986) Clinical and pathological aspects of human African trypanosomiasis (*T.b. gambiense*) with particular reference to reactive arsenical encephalopathy. Am J Trop Med Hyg 35:94–99
94. Pepin J, Milord F (1991) African trypanosomiasis and drug-induced encephalopathy: risk factors and pathogenesis. Trans R Soc Trop Med Hyg 85:222–224
95. Le Bras J, Sina G, Triolo N, Trova P (1977) Symptomatology générale de la trypanosomiase humaine africaine de l'enfant. Med Trop (Mars) 37:51–61
96. Boa YF, Traore MA, Doua F, Kouassi-Traore MT, Kouassi BE, Giordano C (1988) The different present-day clinical picture of human African trypanosomiasis caused by *T.b. gambien*se. Analysis of 300 cases from a focus in Daloa, Ivory Coast. Bull Soc Pathol Exot Filiales 81:427–444
97. Bertrand E, Serie F, Kone I, Rive J, Campaore P, Sentilhes L, Philippe J (1973) Symptomatologie générale de la trypanosomiase humaine africaine au moment du dépistage. Médecine d'Afrique Noire 20:303–314
98. Debroise A, Debroise-Ballereau C, Satge P, Rey M (1968) African trypanosomiasis in young children. Arch Fr Pediatr 25:703–720
99. Ngandu-Kabeya G (1976) Study of the symptomatology of African trypanosomiasis in children (apropos of 24 cases). Ann Soc Belg Med Trop 56:85–93
100. Edan G (1979) Clinical and biological symptoms of *T. gambiense* tryponosomiasis in the meningo-encephalitic period (author's transl). Med Trop (Mars) 39:499–507
101. Ginoux PY, Frezil JL, Alary JC (1982) Symptoms of human trypanosomiasis at the first diagnostic phase in the People Republic of Congo (author's transl). Med Trop (Mars) 42:281–287
102. Antoine P (1977) Neurological and psychological studies of patients with sleeping sickness and their course. Ann Soc Belg Med Trop 57:227–248