

Human African trypanosomiasis in endemic populations and travellers

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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

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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

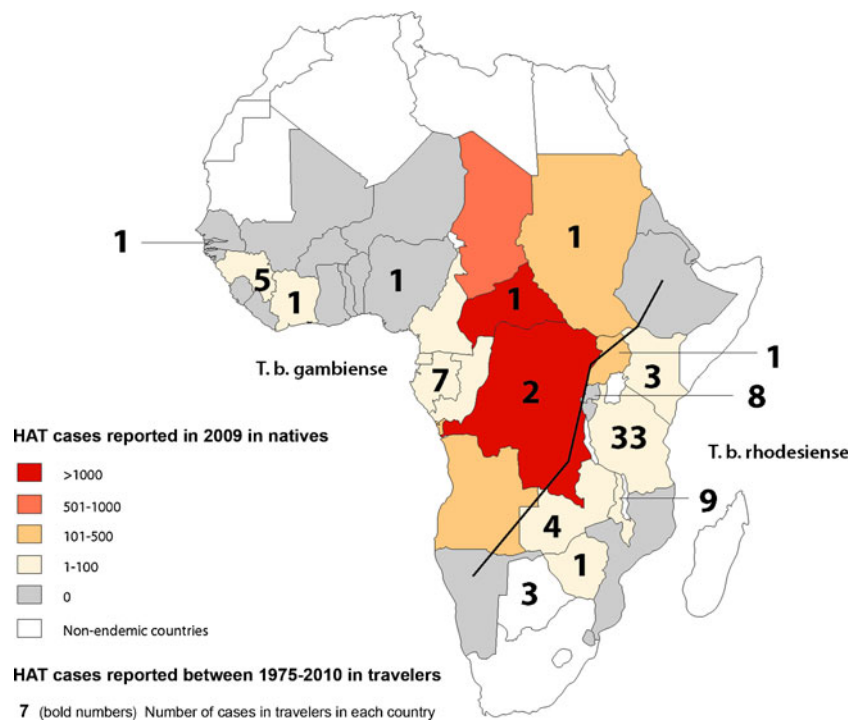
The clinical presentation of HAT depends on the parasite species and on the host (Table 1).

Endemic countries

T.b. gambiense HAT

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

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	<i>T.b. gambiense</i>		<i>T.b. rhodesiense</i>	
		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 ($\geq 37.5^{\circ}\text{C}$)	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]
	Travellers	Generalized 33.3% Satellite (to chancre) 22.2%	Generalized 50% Satellite (to chancre) 50%	Generalized 6.1% Satellite (to chancre) 30.3%	Generalized 33.3% Satellite (to chancre) 16.7%
Sleeping disorder	Natives	Somnolence 18% Insomnia 73% [97]	Somnolence 29–41% [13, 14] Insomnia 25–57% [13, 14, 97]	Somnolence 25–33% [27, 31]	Somnolence 54–66% Insomnia 28–64% [27–30, 33]
	Travellers	Somnolence 0% Insomnia 28.6%	Somnolence 0% Insomnia 16.7%	Somnolence 0% Insomnia 6.7%	Somnolence 16.7% 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 $>5/\text{mm}^3$) 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	<i>T. b. gambiense</i>	<i>T. b. rhodesiense</i>
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].

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