



## Review

# Human African trypanosomiasis: a review of non-endemic cases in the past 20 years

Stephanie J. Migchelsen<sup>a,b</sup>, Philippe Büscher<sup>c</sup>, Andy I.M. Hoepelman<sup>b</sup>, Henk D.F.H. Schallig<sup>a</sup>, Emily R. Adams<sup>a,\*</sup>

<sup>a</sup>Royal Tropical Institute – Biomedical Research, Parasitology, Meibergdreef 39, 1105 AZ Amsterdam, the Netherlands

<sup>b</sup>Department of Internal Medicine and Infectious Disease, University Medical Centre, Universiteit Utrecht, Utrecht, the Netherlands

<sup>c</sup>Department of Parasitology, Institute of Tropical Medicine, Antwerp, Belgium

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## SUMMARY

Human African trypanosomiasis (HAT) is caused by sub-species of the parasitic protozoan *Trypanosoma brucei* and is transmitted by tsetse flies, both of which are endemic only to sub-Saharan Africa. Several cases have been reported in non-endemic areas, such as North America and Europe, due to travelers, expatriots or military personnel returning from abroad or due to immigrants from endemic areas. In this paper, non-endemic cases reported over the past 20 years are reviewed; a total of 68 cases are reported, 19 cases of *Trypanosoma brucei gambiense* HAT and 49 cases of *Trypanosoma brucei rhodesiense* HAT. Patients ranged in age from 19 months to 72 years and all but two patients survived. Physicians in non-endemic areas should be aware of the signs and symptoms of this disease, as well as methods of diagnosis and treatment, especially as travel to HAT endemic areas increases. We recommend extension of the current surveillance systems such as TropNetEurop and maintaining and promotion of existing reference centers of diagnostics and expertise. Important contact information is also included, should physicians require assistance in diagnosing or treating HAT.

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## 1. Introduction

Human African trypanosomiasis (HAT), also known as sleeping sickness, is endemic to sub-Saharan Africa where it is a major threat to public health in 36 countries.<sup>1</sup> It is caused by *Trypanosoma brucei*, a single-celled eukaryotic parasite and member of the Kinetoplastida order.<sup>2</sup> Two subspecies are able to infect humans: *Trypanosoma brucei gambiense* causes a chronic form of HAT in West and Central Africa, while *Trypanosoma brucei rhodesiense* is the pathogenic agent for the more acute form of the disease and is endemic to Eastern Africa.<sup>2,3</sup> The parasite is transmitted by the bite of an infected tsetse fly (genus *Glossina*), and cases of HAT are only found in areas of tsetse fly infestation, which are limited to sub-Saharan Africa. However with the increased movement of people, some travelers, military personnel and immigrants have been reported as HAT-positive. Here, the non-endemic cases of HAT are reported, as well as their frequency and outcome; laboratory

infections with *T. brucei* are considered outside the scope of this review.

The *Trypanosoma* parasites are transmitted through the bite of an infected tsetse fly,<sup>4</sup> and undergo complex changes during their life-cycle alternating between the insect vector and the mammal host. After the parasites are inoculated into man, they proliferate at the infection site, causing an inflammatory nodule or ulcer, also known as a trypanosomal chancre; it is typically described as a circumscribed, red, indurated nodule.<sup>5</sup> Previous studies have shown that the ulcer is much more commonly seen in patients suffering from *T. b. rhodesiense* HAT, with lesions in 70–90% of cases appearing 5–10 days after being bitten by the infected tsetse fly; this is around the same time as fever and detectable parasitemia in the blood.<sup>6</sup> Chancres are rarely seen in *T. b. gambiense* infections, possibly because most infections are detected after the chancre has disappeared.<sup>7</sup>

HAT can be classified into two clinical stages, depending on whether parasites have crossed the blood–brain barrier (BBB) into the central nervous system.<sup>3</sup> After inoculation, trypomastigotes spread via lymph into diverse peripheral tissues and organs initiating the hemolymphatic stage.<sup>8</sup> Diverse clinical symptoms, mostly reflecting inflammatory reactions, may appear, of which

\* Corresponding author. Tel.: +31 20 566 2318; fax: +31 20 697 1841.

E-mail address: [e.adams@kit.nl](mailto:e.adams@kit.nl) (E.R. Adams).

only fever and headache are common in all patients. Up to 50% of European patients develop a rash on the torso and most patients will have swollen, palpable lymph nodes.<sup>9</sup> Patients suffering from *T. b. gambiense* HAT will often show lymphadenopathy, usually on the back of the neck, a condition known as Winterbottom's sign. Parasites can, at this stage, be microscopically detected in blood and lymph node aspirates depending on parasite number.

Signs and symptoms may subside after the acute first stage. In the second stage, also known as the meningo-encephalitic stage, parasites enter the central nervous system.<sup>8</sup> This process occurs within weeks for *T. b. rhodesiense* or months or years after initial infection by *T. b. gambiense*. As the disease progresses, the classical signs of late-stage HAT become apparent:<sup>8</sup> severe headaches, a disruption of the circadian rhythm, with night-time insomnia and daytime somnolence; altered mental functions and personality changes may arise while generalized meningo-encephalitis can lead to coma and death.<sup>4</sup> Other symptoms including anorexia, altered endocrine functions,<sup>10</sup> demyelination and leuko-encephalitis are also typical.<sup>11</sup> It is important to note that not all patients will show the same signs and symptoms of HAT.

## 2. Diagnosis and treatment

Definitive diagnosis relies upon microscopy, however parasite numbers of less than 100 trypanosomes/ml can be difficult to detect with microscopy alone.<sup>7</sup> Concentration methods such as microhematocrit centrifugation,<sup>12</sup> quantitative buffy-coat analysis,<sup>13</sup> or mini-anion exchange columns<sup>14</sup> can be used to concentrate the parasites for easier microscopic detection. In West Africa, many endemic screening programs rely on the card-agglutination test for trypanosomiasis (CATT). The CATT is based on the antibody-mediated agglutination of fixed trypanosomes carrying particular surface glycoproteins and is a sensitive assay to detect *T. b. gambiense*-specific antibodies in blood.<sup>15</sup> *T. b. rhodesiense* lacks these particular surface glycoproteins and thus CATT is not appropriate for the diagnosis of *T. b. rhodesiense* HAT.<sup>16</sup> Patients with *T. b. gambiense* HAT are at risk of misdiagnosis with other infections due to cross-reacting antibodies against *Toxoplasma gondii*, *Strongyloides stercoralis*,<sup>17</sup> Epstein-Barr virus (EBV),<sup>18</sup> cytomegalovirus (CMV),<sup>19</sup> *Plasmodium fieldi*, *Plasmodium brasilianum*, and *Borrelia burgdorferi*.<sup>20</sup> Molecular techniques, such as polymerase chain reaction (PCR), loop-mediated amplification (LAMP) and nucleic acid sequence-based amplification (NASBA) have been developed and evaluated; however, they have yet to be adopted or validated for use in the clinical setting.<sup>4,7,21–23</sup>

To diagnose second-stage HAT, trypanosomes must be microscopically detected in the cerebrospinal fluid (CSF).<sup>24</sup> An elevated ( $>5 \times 10^6/l$ ) number of white blood cells in the CSF is also used to define the second stage of the disease; however this cut-off is sometimes debated.<sup>8</sup>

There are only five licensed drugs for the treatment of HAT.<sup>25</sup> Pentamidine and suramin are available to treat the disease before parasites invade the central nervous system; pentamidine is the recommended drug in the treatment of first-stage *T. b. gambiense* HAT, and suramin is recommended for first-stage *T. b. rhodesiense* HAT.<sup>8</sup> To treat second-stage HAT, drugs that cross the BBB are essential.<sup>4</sup> Melarsoprol is the only drug available to treat *T. b. rhodesiense*-caused HAT and is the most economical,<sup>26</sup> while *T. b. gambiense* HAT can also be cured with eflornithine or a combination of eflornithine and nifurtimox.<sup>27</sup> Melarsoprol is an organo-arsenic compound that causes frequent adverse reactions, which can be severe and even life-threatening. While a comprehensive review on the treatment of HAT is available in Brun et al. 2010,<sup>8</sup> we have included some important contact information for assistance in the diagnosis and treatment at the end of this review.

## 3. Non-endemic clinical cases from the literature

A recent search of PubMed and ProMED-mail, as well as personal communication, resulted in 68 reported cases of HAT in non-endemic countries. Of these, 57 cases were found through a PubMed search (search terms: 'trypanosoma OR HAT OR African trypanosomiasis OR sleeping sickness NOT Chagas NOT animal NOT reservoir') and through a bibliographic search of articles. The search was limited to the past 20 years (1990–2010). Three cases, all related, were found by personal communication (P. Büscher).<sup>28</sup> A ProMED-mail search using 'trypanosomiasis' dating back to 1994 returned 184 reports, however there were only eight additional human cases. Many of these cases were also reported on TropNetEurop ([http://www.tropnet.net/special\\_reports/trypsex\\_serengeti.pdf](http://www.tropnet.net/special_reports/trypsex_serengeti.pdf)), a European surveillance network for imported infectious diseases.

## 4. Non-endemic West African trypanosomiasis

Nineteen cases of non-endemic *T. b. gambiense* HAT were found in the literature search (Table 1). Most of the cases were either immigrants (6/19, 32%) from endemic regions who had migrated to Europe, Australia or North America,<sup>17,19,29,30</sup> or ex-patriots (8/19, 42%) who had been stationed in endemic regions;<sup>18,31–35</sup> the remaining cases were unspecified (5/19, 26%). All described *T. b. gambiense* HAT cases were diagnosed after a considerable time had elapsed after the infection, which is typical for the chronic form.<sup>8</sup> Of the 19 cases of *T. b. gambiense* HAT, nine cases were diagnosed in the first stage of the disease, eight were diagnosed in the second, and two were not specified,<sup>28</sup> but all were successfully treated. Here we discuss selected cases that highlight important observations.

A New Zealand man had been posted in Nigeria and Gabon and was treated in the UK.<sup>31</sup> He was initially diagnosed with and treated for loa loa and schistosomiasis; however splenomegaly, lymphadenopathy, and elevated IgM levels persisted. Trypanosomiasis was suspected, but the positive diagnosis for HAT requires the detection of parasites. Initial examination of lymph, blood, and marrow failed to detect any parasites. Two months after his initial presentation, he returned and trypanosomes were detected in a blood smear and lymph node aspirates. These were presumed to be *T. b. gambiense* given the patient's history. He was treated and cured with suramin and difluoromethylornithine. Individually, these parasitic infections are rarely seen in non-endemic regions; for one patient to be diagnosed with all three seems "most improbable" (Scott, 1991).<sup>31</sup> It is important to remember that travelers to endemic regions may be exposed to many possible parasitic infections. Although one disease may be diagnosed, physicians should consider other possible infections, especially if atypical symptoms are present.

Three cases of *T. b. gambiense* HAT encountered in Portugal may be examples of unusual transmission of the disease.<sup>28</sup> A 30-year-old woman, who had never traveled to an endemic HAT region, was admitted to hospital in Portugal with lesions on her thighs, weakness, and pain. She was clinically and serologically diagnosed with Lyme disease. Fever, leukopenia, and anemia developed, which led to the microscopic examination of tissues, including CSF, where trypanosomes were detected. Both CATT and PCR were positive and indicated infection with *T. b. gambiense*. The patient was treated with eflornithine and was reported to be healthy 3 years later. While determining the route of transmission, it was discovered that her companion, a Brazilian man who had traveled to Angola for a military mission, was an asymptomatic carrier and he was subsequently treated. Sexual transmission was proposed, although sharing of needles during drug abuse cannot be excluded (P. Büscher, personal communication). Furthermore, the woman's

**Table 1**  
Reported non-endemic cases of *Trypanosoma brucei gambiense* human African trypanosomiasis

| Age   | Sex | Nationality                       | Country of exposure      | Year | Clinical features/symptoms  | Diagnosis                     | Stage | Treatment                        | Outcome  | Ref.   |
|-------|-----|-----------------------------------|--------------------------|------|---|-------------------------------|-------|----------------------------------|----------|--------|
| 32    | M   | New Zealander (ex-pat)            | Nigeria, Gabon           | 1991 | Lesion, rash, fever, lymphadenopathy, splenomegaly, elevated levels of IgM                          | Lymph, blood                  | I     | Suramin, difluoromethylornithine | Positive | 31     |
| Young | M   | French (immigrant from Angola)    | Angola                   | 1992 | Fever, insomnia, elevated levels of IgG and IgM   | ND                            | II    | Eflornithine                     | ND       | 19     |
| 52    | F   | Dutch (immigrant from Cameroon)   | Cameroon                 | 1995 | Rash (neck, shoulders), elevated IgM  | CSF                           | II    | Suramin, melarsoprol             | Positive | 29     |
| 32    | M   | Italian (ND)                      | Zaire                    | 1996 | Fever, malaise  | Blood                         | I     | Eflornithine                     | Positive | 46     |
| 45    | M   | French (ex-pat)                   | Gabon                    | 1999 | Lesion, fever, elevated IgM   | Blood                         | I     | Pentamidine                      | Positive | 32     |
| ND    | M   | French (ex-pat)                   | Guinea                   | 2000 | Weakness, sweats, vomiting, myalgia, weight loss, splenomegaly, fever, elevated IgG and IgM, lesion | CSF, blood                    | II    | Eflornithine                     | Positive | 18     |
| 53    | M   | French (ex-pat)                   | Guinea                   | 2000 | Lesion, chills, weakness, fever, lymphadenopathy, hepatosplenomegaly, elevated IgG and IgM          | Blood                         | I     | Pentamidine                      | Positive | 33     |
| 30    | F   | Portuguese                        | Portugal                 | 2001 | Lesion, weakness, fever, leukopenia, anemia   | Marrow, blood, CSF, CATT, PCR | II    | Eflornithine                     | Positive | 28     |
| 19 mo | M   | Portuguese                        | Portugal                 | 2001 | Vertical transmission   | ND                            | ND    | ND                               | Positive | 28     |
| ND    | M   | Brazilian (military)              | Angola                   | 2001 | Asymptomatic carrier  | ND                            | ND    | ND                               | Positive | 28     |
| 42    | M   | Canadian (immigrant from Zaire)   | Zaire                    | 2002 | Insomnia, anorexia, fatigue, headaches, lymphadenopathy, elevated IgM, fever                        | Blood, CSF                    | II    | Eflornithine                     | Positive | 17     |
| 44    | M   | Italian (ND)                      | Gabon                    | 2005 | Fever, headache, weakness, anorexia, lymphadenopathy, hepatosplenomegaly                            | Blood, CSF                    | II    | Eflornithine                     | ND       | 35, 36 |
| 54    | F   | Italian (ND)                      | Central African Republic | 2005 | Fever, headache, insomnia, fatigue, splenomegaly  | Blood                         | I     | Pentamidine, eflornithine        | Positive | 35, 36 |
| 37    | M   | French (ex-pat)                   | Gabon                    | 2007 | Fever, fatigue, anorexia, headache, insomnia, rash, lymphadenopathies                               | Blood, lymph                  | I     | Pentamidine                      | Positive | 34, 35 |
| 72    | M   | French (ex-pat)                   | Gabon                    | 2007 | Pruritus, fever, weakness, anorexia, lymphadenopathy, elevated IgG and IgM                          | Blood                         | I     | Pentamidine                      | Positive | 34, 35 |
| 19    | F   | Australian (immigrant from Sudan) | Uganda                   | 2008 | Lethargy, fever, seizures, cachexia, pruritus, elevated IgG and IgM, encephalopathy                 | CSF                           | II    | Eflornithine                     | Positive | 37     |
| 50    | M   | French (ex-pat)                   | Gabon                    | 2009 | Fever, fatigue, lesion, lymphadenopathy   | Blood                         | I     | Pentamidine                      | Positive | 38, 3  |
| 27    | F   | Dutch (immigrant from Angola)     | Angola                   | 2009 | Fatigue, insomnia, anorexia, depression, coma   | CSF                           | II    | Eflornithine                     | Positive | 30, 39 |
| 24    | F   | Australian (immigrant from Sudan) | Uganda                   | 2009 | Fever, weight loss, seizures, headaches, lymphadenopathy, somnolence                                | Brain biopsy                  | II    | Pentamidine, eflornithine        | Positive | 40     |

M, male; F, female; ND, no data mentioned; CSF, cerebrospinal fluid; CATT, card-agglutination test for trypanosomiasis; PCR, polymerase chain reaction.

19-month-old son was also diagnosed with late-stage sleeping sickness, likely due to vertical transmission, and was successfully treated.

Bisoffi et al. (2005) reported an Italian patient who had reported feeling unwell for over 6 months before seeking treatment. He was diagnosed with second-stage *T. b. gambiense* HAT and eflornithine was requested from the World Health Organization (WHO). The treatment was sent by the WHO, but was subsequently delayed by 9 days while it was held at Italian customs.<sup>36</sup> The patient's symptoms abated once eflornithine treatment was started. While it is unlikely that a 9-day delay caused any significant damage, this case does highlight the importance of having timely access to the required pharmaceutical treatment. Had the patient been suffering from the more acute *T. b. rhodesiense* HAT, it is likely that this 9-day delay could have had severe ramifications, including coma or even death.

In one particular case seen in France,<sup>18</sup> a patient was incorrectly diagnosed with EBV based on antibody detection; in this case the misdiagnosis was due to cross-reactivity. Upon first admission to the hospital, no trypanosomes were detected in the blood. The correct diagnosis of *T. b. gambiense* HAT was not obtained until after emergency hospitalization 6 months later. During the second admission, microscopy of a blood smear and CSF showed trypanosomes. The patient was successfully treated with eflornithine. Physicians should be aware of possible cross-reactions when performing antibody testing.

## 5. Non-endemic East African trypanosomiasis

East African trypanosomiasis is distributed throughout eastern and south-eastern Africa, an area receiving an increasing number of tourists due to the popularity of game reserves.<sup>35</sup> *T. b. rhodesiense* HAT presents more frequently as an acute disease; death can occur less than 2 weeks after infection.<sup>41</sup> The most typical signs are the trypanosomal chancre at the site of the tsetse fly bite and high fever. Forty-nine cases of non-endemic *T. b. rhodesiense* HAT were encountered in the literature search (Table 2). While most of the cases were tourists (34/49, 69%), three of the cases were soldiers (6%) who had been stationed in endemic areas, and 12 (25%) were not specified.

An increase in the number of cases seen in travelers returning to non-endemic areas may serve as a warning of potential outbreaks in a particular region. Such was the case in 2001, when nine patients with HAT (Table 2), were detected in Europe through TropNetEurop.<sup>42–44</sup> Prior to the early 1990s the number of tourists infected with HAT was very low, although Tanzania is endemic for the disease; the sudden rise in non-endemic cases was unusual. All nine patients had traveled to Serengeti and Tarangire National Parks in Tanzania, among other destinations. All patients suffered from fever and most of the patients showed the trypanosomal chancre. Microscopy of blood smears showed trypanosomes. Six patients were treated with suramin during first-stage HAT, however three had multi-organ failure and showed signs of cerebral involvement; these patients were treated with either pentamidine or melarsoprol. Non-specific alternative treatments were used, due to the unavailability of stage-specific medications.<sup>43</sup> One patient, a 53-year-old Dutch woman died of the disease.<sup>44,45</sup> This patient was treated with a single dose of suramin in South Africa and subsequently, melarsoprol treatment was begun. She continued to suffer from headaches, fever, and neurological deterioration. Five days after the last dose of melarsoprol, the patient became paralyzed, went into a coma and required artificial ventilation; she died approximately 4 months later.

Recently, a Dutch traveler was diagnosed with first-stage *T. b. rhodesiense* HAT.<sup>46</sup> She was successfully treated in the Netherlands

and showed complete recovery at the 6-month follow-up. Considering the past outbreak of 2001, this case may be cause for concern.

Within a 1-week period in 2000, two unrelated patients returning from Zambia and Tanzania were admitted to the Hospital for Tropical Diseases in London.<sup>47,48</sup> Both suffered from tsetse fly bites, diarrhea, vomiting, and fever. Upon admission, numerous trypomastigotes were detected in microscopic examination of blood smears. Treatment with suramin was uncomplicated and both patients survived, but significant effort went into obtaining the drugs. Initially, the drug was not available at the hospital's pharmacy or from regional infectious or tropical disease units in the UK, France, or Belgium. A small supply was obtained, after delay, from the Liverpool School of Tropical Medicine, which sufficed until a more complete course was provided by the Centers for Disease Control and Prevention (CDC) in the USA.

A 30-year-old man was admitted to the Institute of Tropical Medicine in Marseille, France after an insect bite while on vacation in Rwanda left him with a severe headache and anorexia.<sup>49</sup> Examination showed hepatosplenomegaly, lymphadenopathy, purpura, and trypanosomes in the CSF. Treatment with prednisolone and melarsoprol was initiated, but twitching and encephalopathy developed after the second course of melarsoprol. Magnetic resonance imaging indicated lesions of the internal capsules and excluded the possibility of post-treatment reactive encephalopathy. Therefore, the treatment was continued, the lesions progressively disappeared, and the patient's prognosis was positive, although the long-term outcome was not specified.

## 6. Discussion

Here, cases of *T. b. rhodesiense* and *T. b. gambiense* HAT in non-endemic areas have been reviewed. HAT, in both clinical forms, is rarely encountered in non-endemic countries; however, continued surveillance and expertise in the diagnosis and management are warranted due to the difficult diagnosis and treatment decisions.<sup>9</sup> Physicians should be aware of the disease and consider HAT in the differential diagnosis if their patient is from or has traveled to an endemic area. Non-endemic cases encountered over the past 20 years have been imported largely due to North Americans, Australians, and Europeans traveling to endemic areas, primarily for safari in game parks, but also military personnel training in endemic areas. As the number of visitors to these game parks is expected to increase, so too is the number of non-endemic cases.<sup>35</sup> Cases are also observed among immigrants arriving from endemic areas and in ex-patriots returning from postings abroad. Interestingly, the epidemiology of HAT seen in non-endemic areas is the opposite of the disease epidemiology seen in Africa. Of the estimated 10 000–30 000 cases in endemic areas of Africa, more than 95% of these cases are due to *T. b. gambiense* HAT.<sup>1</sup> In the cases presented here, approximately 30% of cases were due to *T. b. gambiense* HAT and 70% were due to *T. b. rhodesiense* HAT. This is in agreement with figures from the WHO, showing approximately 20 cases (40%) of *T. b. gambiense* and 30 (60%) of *T. b. rhodesiense* diagnosed per year in non-endemic regions.<sup>9</sup>

According to our review, a common problem in non-endemic regions is an initial misdiagnosis, particularly of *T. b. gambiense* HAT. The chronic nature, characterized by non-specific clinical signs and symptoms, and low parasitemia, may result in the disease remaining undiagnosed and unrecognized for years.<sup>9,33</sup> A number of patients were initially symptomatically diagnosed and/or presumptively treated for malaria,<sup>36,50,51</sup> however as symptoms persist there is a need to reassess the diagnosis. Patients with *T. b. gambiense* HAT have been reported to have antibodies against *T. gondii*, *S. stercoralis*,<sup>17</sup> EBV,<sup>18</sup> CMV,<sup>19</sup> *P. fieldi*, *P. brasiliense*, and *B. burgdorferi*,<sup>20</sup> further complicating diagnosis. This highlights the

**Table 2**  
Reported non-endemic cases of *Trypanosoma brucei rhodesiense* human African trypanosomiasis

| Age        | Sex | Nationality                   | Country of exposure        | Year | Clinical features/symptoms  | Diagnosis                  | Stage | Treatment                         | Outcome  | Ref.      |
|------------|-----|-------------------------------|----------------------------|------|---|----------------------------|-------|-----------------------------------|----------|-----------|
| ND         | M   | Swiss (tourist)               | Rwanda                     | 1990 | “Clinical signs of sleeping sickness”   | Blood, CSF                 | II    | Melarsoprol                       | Positive | 35, 52    |
| ND         | M   | Swiss (tourist)               | Rwanda                     | 1990 | “Clinical signs of sleeping sickness”   | Blood                      | I     | Suramin                           | Positive | 35, 52    |
| 49         | M   | American (tourist)            | Tanzania, Kenya, Rwanda    | 1991 | Fever, lesion, lymphadenopathy, chills, sweat, anorexia, malaise, diarrhea                    | Blood                      | I     | Pentamidine, suramin              | Positive | 53        |
| ND         | M   | French (soldier)              | Rwanda                     | 1994 | Meningoencephalitis   | CSF                        | II    | Melarsoprol                       | Positive | 54        |
| ND         | M   | French (soldier)              | Rwanda                     | 1994 | Major inflammatory syndrome   | Blood, medulla             | II    | Melarsoprol                       | Positive | 54        |
| 57         | M   | Mexico (tourist)              | Kenya                      | 1996 | Fever, headache, lesion, hepatic dysfunction, respiratory distress                            | Blood, lesion exudate, CSF | II    | Pentamidine, melarsoprol          | Positive | 55        |
| 30         | M   | French (tourist)              | Rwanda                     | 1997 | Headache, weight loss, fever, hepatosplenomegaly, lymphadenopathy                             | Blood, marrow, CSF         | II    | Melarsoprol                       | Positive | 49        |
| 41         | M   | American (tourist)            | Tanzania                   | 1999 | Weakness, headache, fever, chills, sweats, anorexia, lesion, lymphadenopathy                  | Blood, CSF                 | II    | Suramin, melarsoprol              | Positive | 56        |
| 54         | F   | American (tourist)            | Tanzania                   | 1999 | fever, sweats, chills, myalgia,   | Blood                      | I     | Suramin                           | Positive | 24        |
| 49         | M   | American (tourist)            | Tanzania                   | 1999 | Malaise, drowsiness, insomnia, fever, chills, sweats, headache, myalgia, lesion               | Blood                      | I     | Suramin                           | Positive | 24        |
| 47         | F   | German (tourist)              | Zambia, Zimbabwe, Tanzania | 2000 | Fever, insomnia, jaundice, lesion, lymphadenopathy, mucosal hemorrhage, splenomegaly, ascites | Blood, marrow              | I     | Suramin                           | Positive | 57        |
| 30         | F   | Australian (tourist)          | East Africa                | 2000 | Fever, rigors, headache, nausea, vomiting, myalgia, splenomegaly                              | Blood                      | I     | Pentamidine, suramin              | Positive | 58        |
| 51         | M   | British (tourist)             | Zambia                     | 2000 | Lesion, myalgia, diarrhea, fever, vomiting, headache, rigors, sweats                          | Blood                      | I     | Suramin                           | Positive | 47, 48    |
| 30         | M   | British (tourist)             | Kenya, Tanzania            | 2000 | Lesion, fever, diarrhea, vomiting   | Blood                      | I     | Suramin                           | Positive | 43, 44    |
| 30         | F   | Australian (tourist)          | Tanzania                   | 2000 | Fever, rigor, headache  | Blood                      | I     | Pentamidine, suramin              | Positive | 59        |
| 32         | M   | ND (treated in Antwerp)       | Tanzania                   | 2001 | Fever, chancre, headache, jaundice, hepatosplenomegaly  | Blood                      | I     | Suramin                           | Positive | 60        |
| 33         | M   | Italian (tourist)             | Tanzania                   | 2002 | Fever, headache, nausea, vomiting, skin lesion, lymphadenopathy                               | Blood                      | I     | Pentamidine, suramin              | Positive | 42, 43    |
| 30         | M   | Italian (tourist)             | Tanzania                   | 2002 | Skin lesion, local edema, fever, mild jaundice, multi-organ failure, hepatomegaly             | Blood                      | I     | Pentamidine                       | Positive | 42, 43    |
| 37         | M   | American (tourist)            | Tanzania (Kenya, Zimbabwe) | 2002 | Fever, lesion, headache, fatigue, myalgia, vomiting, rash                                     | Blood                      | I     | Suramin                           | Positive | 26        |
| 7 patients |     | American/ Canadian            | Tanzania                   | 2002 | ND  | ND                         | ND    | ND                                | ND       | 26        |
| 44         | F   | British (tourist)             | Tanzania                   | 2002 | Lesion, fever   | ND                         | II    | Pentamidine                       | Positive | 43        |
| 41         | M   | Swedish (tourist)             | Tanzania                   | 2002 | Lesion, fever   | ND                         | I     | Suramin                           | Positive | 43        |
| 68         | M   | South African (tourist)       | Tanzania                   | 2002 | Fever, renal failure, acidosis, jaundice  | ND                         | II    | Melarsoprol                       | Positive | 43        |
| 27         | F   | Norwegian (researcher)        | Tanzania                   | 2002 | Lesion, fever   | ND                         | I     | Suramin                           | Positive | 43        |
| 60         | M   | Dutch (tourist)               | Tanzania                   | 2002 | Fever   | Blood                      | I     | Suramin                           | Positive | 43, 44    |
| 55         | F   | Dutch (tourist)               | Tanzania                   | 2002 | Lesion, fever, headache   | Blood                      | I     | Suramin                           | Positive | 39, 40    |
| 53         | F   | Dutch (tourist)               | Tanzania                   | 2002 | Lesion, fever, headache, intracerebral manifestations, coma                                   | Blood                      | II    | Suramin, melarsoprol              | Death    | 35, 43–45 |
| 28         | M   | Dutch (tourist)               | Kenya, Tanzania            | 2003 | Fever, headache, myalgia, vertigo   | Blood                      | I     | Suramin                           | Positive | 61        |
| 9          | M   | British (tourist)             | Tanzania                   | 2004 | Lesion, fever, dry cough, vomiting  | Lesion aspirate            | I     | Suramin                           | Positive | 62        |
| 14         | M   | British (tourist)             | Tanzania                   | 2004 | Abdominal pain, fever, lesion, dry cough, vomiting, lymphadenopathy                           | Blood, lesion aspirate     | I     | Suramin                           | Positive | 62        |
| 26         | M   | British (soldier)             | Malawi                     | 2006 | Insomnia, lethargy, vomiting, chancre, lymphadenopathy, fever, rigors                         | Blood                      | I     | Suramin                           | Positive | 63        |
| 25         | F   | Australian (tourist)          | Malawi                     | 2006 | Fever, rigors, nausea, vomiting, diarrhea   | Blood                      | I     | Suramin                           | Positive | 64        |
| 31         | M   | Australian (tourist)          | Malawi                     | 2006 | Fever, myalgia, rigors, vomiting  | Blood                      | I     | Suramin                           | Positive | 64        |
| 62         | F   | American (tourist)            | Africa                     | 2006 | Fever, lesion, elevated IgM, rash   | Blood                      | II    | Pentamidine, suramin, melarsoprol | Positive | 54, 55    |
| 4 patients | ND  | Canadian, British, Australian | Malawi                     | 2007 | Thrombocytopenia, hallucinations  | Blood                      | I     | Suramin                           | ND       | 67        |

**Table 2** (Continued)

| Age | Sex | Nationality       | Country of exposure                       | Year | Clinical features/symptoms  | Diagnosis  | Stage | Treatment  | Outcome  | Ref.   |
|-----|-----|-------------------|---|------|---|------------|-------|--|----------|--------|
| 38  | M   | British (tourist) | Namibia, Mozambique, Malawi, South Africa | 2007 | 1) Fever, lymphadenopathy, hepatomegaly 2) Somnolence, myalgia, headache, sweats 3) Somnolence, headache, fevers, nerve palsy | Blood, CSF | II    | 1) Suramin, melarsoprol 2) Eflornithine 3) Suramin, melarsoprol, pentamidine | Positive | 68     |
| 44  | F   | German (tourist)  | Tanzania                                  | 2009 | Lesion, fever, myalgia, malaise, diarrhea, convulsions  | Blood      | II    | Suramin, melarsoprol   | Death    | 35, 41 |
| 25  | F   | Dutch (tourist)   | Tanzania                                  | 2009 | Fever, lymphadenopathy, lesion, headache  | Blood      | I     | Suramin  | Positive | 69     |
| 61  | M   | Polish (tourist)  | Uganda, Rwanda                            | 2009 | Fever, multi-organ failure, asthenia, lesion, chills, jaundice, respiratory distress, hepatosplenomegaly, mucosal hemorrhage  | Blood      | I     | Pentamidine  | Positive | 70     |
| 30  | F   | Dutch (tourist)   | Tanzania                                  | ND   | Fever, chancres, jaundice   | Blood      | I     | Suramin  | Positive | 46     |

M, male; F, female; ND, no data mentioned; CSF, cerebrospinal fluid.

shortcomings of serological testing and emphasizes the need for better and more sensitive means of detection in blood and CSF.<sup>71</sup> In this review it was found that diagnoses were based on symptoms and microscopic detection of parasites in blood, lymph, or CSF. Only one patient was confirmed using CATT and in only three cases was PCR used to confirm the diagnosis,<sup>17,28,68</sup> showing that molecular or serological techniques have not replaced classic parasitological techniques even in countries where equipment is available<sup>3</sup> (Tables 1 and 2).

A further problem complicating the management of patients is the availability of drugs to treat HAT. Important to note is that, thanks to the donations of Aventis and Bayer, all drugs for the treatment of sleeping sickness are now readily available from the WHO office in Geneva (contact: SimarroP@who.int at WHO HTM/NTD/IDM, Via Appia, Geneva, Switzerland), directly or via national pharmacies. The CDC provides all pharmaceuticals to treat HAT in the USA. As such, it maintains records of all HAT patients treated. The disease is rare in the USA;<sup>72</sup> only 14 cases were diagnosed and treated between 1968 and 1985,<sup>73</sup> and less than 10 were reported during the two-decade period of this search.<sup>24,26,53,56,65,66</sup> With such a centralized system for the distribution of medication, any increase in cases would hopefully become immediately apparent.

Many physicians still face difficulties acquiring suramin or melarsoprol to treat their patients, highlighting the need for easy access to these drugs.<sup>47</sup> Due to the fact that HAT is classified as a neglected tropical disease (NTD),<sup>74</sup> there is little incentive for pharmaceutical companies to invest in research, development, or production of new anti-trypanosomal compounds, as those most in need of the drug are not able to pay for treatment. In 2001 the WHO, along with several international and non-governmental organizations<sup>75</sup> convinced Aventis, the pharmaceutical company that manufactures pentamidine, melarsoprol, and eflornithine, to guarantee a free production of these drugs.<sup>76</sup> Storage and transport of the drugs is to be overseen by Médecins Sans Frontières (MSF). Bayer has also agreed to provide free production of suramin and continue production of nifurtimox. Similarly, the pharmaceutical industry should be encouraged to develop new effective medications and provide them at an affordable cost. However, long-term availability of all trypanocides, for both the endemic and non-endemic countries, is still uncertain.<sup>26</sup>

Before embarking on travel to endemic areas, travelers should be warned of the possible risks of HAT. General recommendations to prevent tsetse fly bites include wearing light-colored clothing that fully covers the arms and legs,<sup>53</sup> as well as the use of personal insecticides. The most effective means for preventing trypanosomiasis, both in travelers and in those living in endemic areas, is the control and reduction of vectors and reservoirs. Those advising and treating travelers, whether primary care physicians or specialists at a tropical center, should be vigilant for this disease. However, since the vector is only present in sub-Saharan Africa, climate change should not affect HAT as may be seen in other infectious diseases such as Chikungunya by virus-carrying *Aedes* mosquitoes.

In 2001 the cluster of HAT cases in European travelers<sup>43</sup> acted as an alarm system for an increase in cases in Tanzania. By using ProMED-mail and TropNetEurop as a surveillance tool for tropical diseases the awareness of clinicians in both non-endemic and endemic settings was increased. Information from this cluster of cases was passed on to the Tanzanian Government to increase vigilance in the affected region, which led to an increase in vector control and surveillance programs.<sup>43</sup> Currently TropNetEurop does not report HAT cases and was only involved in 2001 due to the unusually large outbreak. We recommend the expansion of TropNetEurop to monitor HAT cases in Europe; in this manner, potential outbreaks can be detected and a warning can be sent to developing countries that might otherwise be unaware of the situation.<sup>77</sup>

In conclusion, although there are relatively few cases of non-endemic HAT, it is essential that knowledge and expertise of diagnostics and treatment are made available in non-endemic regions so that when cases occur, they can be rapidly and effectively diagnosed and treated. This should include the use of diagnostic algorithms since HAT is often not suspected in the first instance. We recommend the use of reference centers at tropical departments in hospitals or institutes in non-endemic countries, where diagnostic expertise, tests, and access to treatments are available. Such institutions will hopefully be able to ensure availability of drugs essential in the management of HAT under the new drug distribution policy of the WHO.

Surveillance networks, such as ProMED-mail and TropNetEurop should be maintained and expanded to ensure access to institutional databases. Currently TropNetEurop is limited to European collaborating centers and only reports on three imported diseases: malaria, schistosomiasis, and dengue fever. We recommend expanding the list of imported diseases that TropNetEurop monitors and allowing public access to this database. Due to the success of surveillance systems in Western countries, the possibility of introducing similar 'alarm' systems for HAT in Africa should be explored.

## 7. For further assistance

Assistance in diagnosis can be requested from the WHO Collaborating Centre for Research and Training on Human African Trypanosomiasis Diagnostics at the Institute of Tropical Medicine, Antwerp (contact: Philippe Büscher, pbuscher@itg.be).

All drugs are available from the WHO office in Geneva and via national pharmacies. Contacting this office (Dr Pere Simarro and Dr Jose Ramon Franco) enables the WHO to keep records of imported HAT.

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