Treatment of human African trypanosomiasis—present situation and needs for research and development

Dominique Legros, Gaëlle Ollivier, Marc Gastellu-Etchegorry, Christophe Paquet, Christian Burri, Jean Jannin, and Philippe Büscher

Human African trypanosomiasis re-emerged in the 1980s. However, little progress has been made in the treatment of this disease over the past decades. The first-line treatment for second-stage cases is melarsoprol, a toxic drug in use since 1949. High therapeutic failure rates have been reported recently in several foci. The alternative, eflornithine, is better tolerated but difficult to administer. A third drug, nifurtimox, is a cheap, orally administered drug not yet fully validated for use in human African trypanosomiasis. No new drugs for second-stage cases are expected in the near future. Because of resistance to and limited number of current treatments, there may soon be no effective drugs available to treat trypanosomiasis patients, especially second-stage cases. Additional research and development efforts must be made for the development of new compounds, including: testing combinations of current trypanocidal drugs, completing the clinical development of nifurtimox and registering it for trypanosomiasis, completing the clinical development of an oral form of eflornithine, pursuing the development of DB 289 and its derivatives, and advancing the pre-clinical development of megazol, eventually engaging firmly in its clinical development. Partners from the public and private sector are already engaged in joint initiatives to maintain the production of current drugs. This network should go further and be responsible for assigning selected teams to urgently needed research projects with funds provided by industry and governments. At the same time, on a long term basis, ambitious research programmes for new compounds must be supported to ensure the sustainable development of new drugs.

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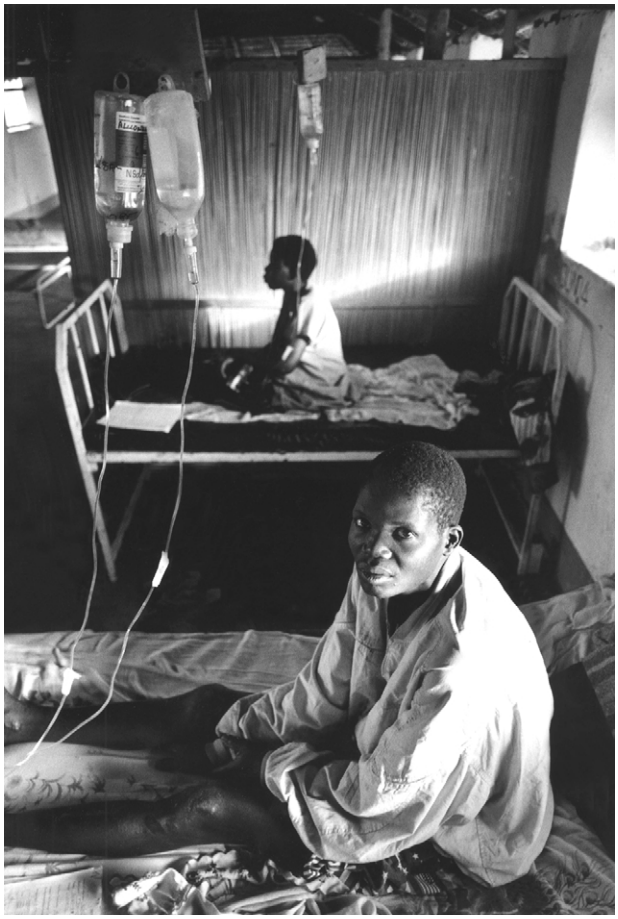

Tom Stoddart/IPG

Sleeping sickness victim in hospital in Omugo, northern Uganda.

Introduction

Human African trypanosomiasis (HAT), or sleeping sickness, is a tropical disease transmitted through the bites of infected tsetse flies. The disease was largely controlled in the 1960s, but a lack of human and financial resources put into combating the disease, and years of conflict in the most affected countries (and resultant disruption of health infrastructures and population displacement) have hampered efforts to monitor and control the disease. As a result, the disease re-emerged in the 1980s,[1] and today 60 million people are exposed to HAT (figure).[1] 36 000 cases were reported to the WHO in 1998, but only 3–4 million people are under surveillance and it is estimated that 300 000 people are infected.[1] Angola, the Democratic Republic of Congo (DR Congo), and Sudan are most affected, and prevalence has also increased in the Republic of Congo and in the Central African Republic.

There are two forms of HAT caused by two morphologically identical parasites: *Trypanosoma brucei*

DL is at Epicentre, Paris, France, and at the DND Working Group/Médecins Sans Frontières, Geneva, Switzerland; GO is at Epicentre, Paris; MGE is at Médecins Sans Frontières, Paris; CP is at the Institut de Veille Sanitaire, Paris; CB is at the Swiss Tropical Institute, Basel, Switzerland; JJ is at the World Health Organisation, Geneva, Switzerland; and PB is at the Institute of Tropical Medicine, Antwerp, Belgium.

Correspondence: Dr Dominique Legros, Epicentre, 8 rue Saint Sabin, 75011 Paris, France. Tel +33 1 40 21 28 48; fax +33 1 40 21 28 03; email dlegros@epicentre.msf.org

gambiense HAT is primarily a human chronic disease, endemic in west and central African countries; *Trypanosoma brucei rhodesiense* HAT has a huge animal reservoir and is primarily zoonotic. It causes acute illness in people in eastern and southern African countries.

Both forms of HAT have two clinical stages. The first often goes undiagnosed and corresponds to the multiplication of trypanosomes in the blood and lymphatic system. When the parasites cross the blood-brain barrier, the disease progresses to the second stage, which is characterised by neurological symptoms and, without treatment, evolves towards body wasting, somnolence, coma, and death. Clinical presentation and serological tests lack specificity for diagnosis, which is based on the detection of trypanosomes in the lymph nodes, blood, and cerebrospinal fluid. The definition of the disease stage relies on parameters related to the cerebrospinal fluid conditions (cytorachia, parasite presence, proteinorachia).

Control of gambiense HAT is undertaken through case detection and treatment alone. Cases are detected either by active case-finding via mobile teams or when patients present spontaneously to health structures (passive case-finding). After detection, most cases are treated in specialised centres. Once treated, patients are followed up for 2 years. For rhodesiense trypanosomiasis, vector-control activities (sterile tsetse flies, impregnated flytraps) yield good results for the control of both the animal and the human disease. Such activities seem to be less effective and are not widely applied for the control of gambiense HAT; however, they might become more relevant because of the scarcity of effective drugs. No vaccine is expected in the near future.

Current treatment

Drugs to treat HAT are old, scarce, highly toxic, and encounter parasite resistance. The treatment of HAT is stage specific. The drugs used for the first stage—pentamidine and suramin—were both developed more than half a century ago (table 1). Pentamidine has been used since 1940 for *T b gambiense* HAT and is usually well tolerated, with hypotension and hypoglycaemia as the most common reported side-effects. The present recommended regimen is seven to ten doses of 4mg/kg per day given intramuscularly once daily or every other day. Suramin has been used since the early 1920s for the treatment of early stage *T b rhodesiense* HAT only. The typical protocol is 5 mg/kg at day 1, 10 mg/kg at day 3, and 20 mg/kg at days 5, 11, 23, and 30, given by slow intravenous injection. Severe side-effects have often been reported, including anaphylactic shocks, severe cutaneous reactions, neurotoxic signs, and cases of renal failure.

Three drugs are used to treat second-stage sleeping sickness: melarsoprol, eflornithine, and nifurtimox (table 1). Melarsoprol is an organo-arsenical compound that has been in use since 1949 for both forms of HAT. The most common treatment protocol consists of three to four series of three or four injections (one intravenous injection per day) separated by rest periods. An alternative protocol for *T b gambiense* HAT has recently been proposed, based on pharmacokinetic investigations.[2] It consists of ten consecutive injections of 2·2 mg/kg per day. Preliminary results suggest a similar efficacy but a higher, non-significant proportion of adverse skin reactions when compared with the standard protocol.[3] Melarsoprol is a highly toxic drug. The most serious adverse drug reaction is reactive encephalopathic syndrome, which happens in 5–10% of cases with an average case-fatality rate of 50%.[4] To prevent the occurrence of this syndrome, prednisolone is often co-administered with melarsoprol. In addition, high therapeutic failure rates have been reported recently in northwest Uganda (30·4% within 2 years[5]), northern Angola (25% within 30 days[6]), and Sudan (18% at 6 months, MSF unpublished data). The high therapeutic failure rate reported in northern Uganda might be due to the appearance of strains of trypanosomes with reduced sensitivity to melarsoprol.[7] The mechanism of resistance is unknown.

Eflornithine (DL-alpha-difluoromethylornithin) is the only new molecule registered for the treatment of HAT over the past 50 years. It has been used successfully in the treatment of second stage *T b gambiense* patients since the 1980s,[4] but seldom for *T b rhodesiense* HAT, which is more resistant to this drug than *T b gambiense*.[8] Eflornithine is difficult to administer, requiring 400 mg/kg per day in four daily infusions for 7 or 14 days. It is better tolerated than melarsoprol, but can cause pancytopenia, diarrhoea,

Table 1. Overview of trypanocidal drugs

Drug	Species	Indication	Year of first use	Structure [half life]	Comments
Pentamidine isethionate	*T b gambiense*	Stage 1	1940	Aromatic diamine [9·4 hours by IM] [6·4 hours by IV]	
Suramin sodium	*T b gambiense* *T b rhodesiense*	Stage 1	Early 1920s	Sulphonated naphtylamine [50 days]	
Melarsoprol (Mel B)	*T b gambiense* *T b rhodesiense*	Stage 2	1949	Trivalent organic arsenical (biological activity) [35 hours]	Increase treatment failure (resistant strains?)
Eflornithine	*T b gambiense*	Stage 2	1981	DL-alpha-difluoromethylornithine [3 hours]	Difficult use
Nifurtimox	*T b gambiense* *T b rhodesiense ?*	Stage 2	1977	5′-nitrofurane [3·5 hours]	Not registered for HAT Case series only Toxicity and action on *T b rhodesiense* poorly documented

IM=intramuscular, IV=intravenous

Table 2. Results of case series with nifurtimox among patients with *T b gambiense* HAT

Protocol		Patients	Successes	Relapses	Deaths	Reference
mg/kg/day	Duration (days)					
12–17	60	19 MR	7 followed-up	12	0	12
Adults : 15 Children : 20	30	22 (5NC + 17 MR)	2 < 24 months 15 at 24 months	1	1	13
Adults : 15 Children : 20	30	75 (9NC + 66 MR)	9 < 24 months 45 at 24 months	5	5	13
30	30	27 MR	16 followed-up	9	2	14
6	40–120	4	2 at 10 months 1 at 48 months	1	0	15
Adults : 12.5–15 Children : 15–20	60	15 (7 NC + 8 MR)	NC: 5 at 30 months MR: 7 at 30 months	1	1	16

NC=new cases, MR=melarsoprol-refractory

convulsions, and hallucinations. All adverse reactions are reversed if treatment is discontinued.[4] Clinical investigations with an oral formulation are continuing under the WHO's Special Programme for Research and Training in Tropical Diseases. Although a higher relapse rate and a higher frequency of diarrhoea have been reported compared with the intravenous form,[9,10] oral administration would greatly facilitate the practical use of eflornithine in resource-poor settings and its clinical development should be completed.

Nifurtimox is a cheap, orally administered drug used to treat American trypanosomiasis (Chagas disease).[11] In a series of small-scale studies (less than 200 cases) in the 1980s and 1990s, nifurtimox showed contradictory results in the treatment of *T b gambiense* HAT (table 2).[12–16] No treatment schedule has been validated yet. The protocol most widely used today is 15 mg/kg per day in three doses for 2 weeks in adults and 20 mg/kg per day in three doses over the same period in children under 15 years of age. The type and frequency of adverse reactions are poorly documented, although toxicity seems to increase with dose and duration of treatment.[14,15] Anorexia and neurological side-effects are common. Nifurtimox could represent an effective therapeutic alternative, especially in combination with other drugs, at least for gambiense sleeping sickness. However, efficacy and safety should be assessed in randomised, controlled clinical trials.

Therapeutic perspectives

The treatment of HAT is hampered by the limited number and the toxicity of trypanocidal drugs and their difficult administration, as well as by the increasing number of treatment failures. This situation calls for more research and development towards new protocols (combination treatments) in the immediate term, together with the clinical development of promising compounds to ensure new drug availability in the longer term.

Combination treatments

It is widely accepted that combination treatments involving existing drugs delay the occurrence of resistance. For HAT, they might also improve the efficacy of treatment and if synergistic, allow a reduction of the dosages and possibly of the toxicity of the drugs. However, only a few combinations have been used on a compassionate basis in people and our knowledge of the efficacy and safety of these protocols is too limited to recommend their systematic use. For early stage *T b gambiense* cases, 616 patients have been treated with a combination of pentamidine and suramin between 1983 and 1992 in the former Zaire, with no improvement of the cure rate.[17] For late-stage *T b gambiense* infection, one patient was reported fully treated with a combination of eflornithine and melarsoprol in Equatorial Guinea in 1996 after several ineffective cures of melarsoprol and of oral eflornithine.[18] In DR Congo, in 68 patients treated with a combination of nifurtimox and melarsoprol in 1998, no case of failure was recorded until 24 months of follow up (P Büscher, unpublished observation). In northern Uganda, in 53 cases of melarsoprol failure treated with the same combination between September 1999 and June 2000, six relapses and three deaths (two in hospital and one during follow-up) had been recorded after 1 year of follow-up (MSF unpublished data). For late-stage *T b rhodesiense* infection, therapeutic combinations of suramin with eflornithine and suramin with metronidazole have been tested with some success although in very limited case series.[19–21]

Drugs in development

Two drugs have potential as effective treatments for sleeping sickness. DB 289 is a diamidine derivative, currently being developed for use against *Pneumocystis carinii*. The compound is a prodrug of an active metabolite and can be orally administered. It has shown good activity against African trypanosomes in vitro as well as in different animal models in the first stage of HAT. Phase I clinical trials have been recently concluded and no significant adverse drug reactions were noted. A phase IIA trial (proof of principle, first application in HAT patients) has started in Angola and DR Congo. Further derivatives of the same class of compound are under investigation for activity in the late stage of HAT (C Burri, unpublished observation). Even if all clinical trials are successful, DB 289 will not reach the market for at least 5 years.

Megazol is a nitro-imidazole synthesised in 1968 but discarded because of its mutagenicity (positive Ames test). This compound, which partly crosses the blood-brain barrier in primates,[22] has been reinvestigated effectively in animal models in the past years. In 1998, a megazol with suramin

combination was seen to be effective in a long-term experimental mouse model of late-stage HAT.[23] More recently, megazol was tested in vervet monkeys infected with *T b gambiense*. Further development of megazol will depend on the outcome of the detailed toxicological assessment.

No other substance is anywhere near preclinical or clinical development. Therefore, there could soon be no further effective drugs on the market to treat HAT patients, especially the second-stage cases, and additional research and development efforts are urgently required.

Research and development priorities

Several years and substantial resources are needed to develop a compound up to registration. In addition, conditions for field research for trypanocidal drugs are far less than optimum. Only a few operational treatment centres offer both sufficient recruitment capacities and adequate technical competence, together with a stable political environment for field research projects. At the same time, it is increasingly difficult for the few trypanosomiasis specialists to obtain funds and/or institutional support for applied research. Choices must therefore be made to agree on crucial research projects.

We regard the following to be the current research and development priorities in the domain of HAT therapy: (1) testing combinations of current trypanocidal drugs in vitro for drug synergy and in phase II and phase III clinical trials; (2) pursuing the clinical development of nifurtimox with the objective of registration for HAT; (3) completing the clinical development of oral eflornithine; (4) pursuing the development of DB 289 and its derivatives; and (5) concluding the preclinical development of megazol, and eventually engaging in its clinical development.

Partners from the public sector (WHO, governments, academia) and from the private sector (industry, non-governmental organisations) are already engaged in joint initiatives to maintain the production of current drugs. This network should also be responsible for assigning selected teams to the research projects according to treatment priorities. Funds, provided by industry and governments, should be allocated to support the rehabilitation of treatment centres in epidemic foci and the implementation of field research. In the short-term, research is needed to adapt drug formulations for use in field conditions and combine drugs to protect against resistance. At the same time, long-term research and development projects should be launched as the only way to ensure a sustained pipeline of new treatments. Greater public sector involvement is urgently needed in both the developed and less-developed world if we are to guarantee a sustainable supply of treatment options solution for this neglected disease.

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Conflict of interest

JJ coordinated the World Health Organisation /Aventis sleeping sickness drug availability project within the WHO. We have no other conflicts of interest to declare.

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