

# Availability and affordability of treatment for Human African Trypanosomiasis

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## Summary

Human African Trypanosomiasis (HAT) is a re-emerging disease whose usual treatments are becoming less efficient because of the increasing parasite resistance. Availability of HAT drugs is poor and their production in danger because of technical, ecological and economic constraints. In view of this dramatic situation, a network involving experts from NGOs, WHO and pharmaceutical producers was commissioned with updating estimates of need for each HAT drug for the coming years; negotiations with potential producers of new drugs such as eflornithine; securing sustainable manufacturing of existing drugs; clinical research into new combinations of these drugs for first and second-line treatments; centralizing drug purchases and their distribution through a unique non-profit entity; and addressing regulatory and legal issues concerning new drugs.

**keywords** Human African Trypanosomiasis (HAT), HAT pharmaceuticals, distribution strategy

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## Introduction

Human African Trypanosomiasis (HAT) or sleeping sickness is a parasitic disease transmitted to man through the bite of a tsetse fly. At the early or first stage the features of the disease – recurrent fever, pain, weakness – are not specific apart from enlarged posterior cervical adenopathy. Then, systemic manifestations occur, and at the second stage the central nervous system becomes affected, leading to intense suffering with severe psychiatric and neurological disturbances followed by cachexia, coma and ultimately death. HAT is invariably fatal if untreated.

There are two forms of HAT, each caused by a different parasite. *Trypanosoma brucei gambiense* causes a chronic infection lasting years and affecting countries of western and central Africa. Its reservoir is mainly human. *T. b. rhodesiense* causes acute illness lasting several weeks or months in countries of eastern and southern Africa, fuelled by a large animal reservoir. Thirty-six countries in West, East, Central and southern Africa are affected; hence 55 million people are at a risk of contracting the disease, but only 4 million are under surveillance. Thus the 25 000–40 000 cases reported

annually represent only part of the true caseload – the real incidence could be as many as 300 000–500 000 new cases per year and the number of patients dying may be as high as 60 000 per year (WHO 1996).

By 1960, thanks to control programmes, most African countries reported less than one to two new cases per 10 000 people every year. Over the last 15 years, the disease has been flaring up again, because of a decline in surveillance and control programmes and population displacements, often linked to war. This is a spectacular rebound; outbreaks frequently occur and 10–30% of the population can be affected in some areas.

## Treatments

Treatment differs according to the stages, related to the capacity for the drug to go through the blood–brain barrier. It may also differ according to the parasite.

Pentamidine isethionate is used for the treatment of early stage HAT caused by *T. b. gambiense* infection. It is administered daily or every other day by intramuscular injection, 7–10 injections at a dose of 4 mg base per kg

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body weight. Most frequent adverse reactions are hypertension, abdominal pain, vertigo, hypersalivation and mild nephrotoxicity, generally reversible. The drug is commercially available at US\$ 8–14 per vial from Sedapharm (France) and Schein (USA). Due to a special agreement with Rhône-Poulenc Rorer (now Aventis), it is available through WHO at US\$ 3 per vial for treating HAT.

Suramin sodium (Germanin<sup>®</sup>) is used for the treatment of early stage HAT as a result of *T. b. rhodesiense* infection. It is administered by a single weekly intramuscular injection for 6 weeks at a dose of 1 g per injection. Most frequent adverse reactions are nausea, vomiting, urticaria and less often renal damage and exfoliative dermatitis. Suramin sodium is commercially available at US\$ 8 per vial from Bayer (Germany).

Melarsoprol (Arsobal<sup>®</sup>) is used for treatment of the second stage of the disease, when the central nervous system is affected, in both *T. b. gambiense* and *T. b. rhodesiense* infections. It is administered intravenously usually in three series of three injections each, with a 7–10-day rest period between series. The final dose is 3.6 mg per kg body weight. Several protocols have been developed in an attempt to curb the severe adverse reactions: myocardial damage, hypertension and exfoliative dermatitis. The most serious side-effect is reactive encephalopathy, which occurs in 5–10% of patients treated with melarsoprol; the case fatality ratio is around 50%. The drug is commercially available at US\$ 8 per vial from Sedapharm (France).

Eflornithine (Ornidyl<sup>®</sup>) is used in the treatment of second stage HAT caused by *T. b. gambiense* infection and the only registered drug available for the treatment of patients not responding to melarsoprol. It is administered by intravenous infusion at a dose of 400 mg per kg body weight evenly divided into four daily infusions (every 6 h) for 7 or 14 days. Studies have shown that the 7-day schedule is suitable in cases where melarsoprol has failed; 14 days is used in first-line treatment. Adverse reactions are mild and reversible: diarrhoea, seizure, anaemia, thrombocytopenia, vomiting and fever. Marion Merrell Dow stopped production when it merged with Hoechst and Roussel.

#### **Affordability and availability of these treatments and reactions**

In 1999, alarming news came from pharmaceutical companies. The agreement concerning pentamidine isethionate was revised by Aventis (Rhône-Poulenc Rorer merged with Hoechst Marion Roussel), proposing a progressive substantial cost increase. On several occasions, Bayer, which maintained suramin production on the grounds that no alternatives were available, threatened to stop it. They had

also planned to stop nifurtimox production. Problems in Europe over manufacturing the raw materials required for melarsoprol (containing arsenic, which is highly controversial for ecological reasons) have rendered its production uncertain.

In the field, treatments rely on old drugs discovered between 1922 and 1949 which are very toxic and difficult to administer. A new drug was introduced in 1986 but its production has been stopped. In fact, despite the re-emergence of this disease, production of all HAT drugs is in danger. Moreover, the standard treatment for second-stage HAT, melarsoprol, is losing efficacy as a result of resistance and relapses, especially in Angola, Southern Sudan, Congo and northern Uganda where 25–30% of patients treated with melarsoprol relapse (Legros *et al.* 1999). These recent studies are worrying: they show that treatment failures are directly because of the parasite, not the environment or the patients. This means possible transmission and further extension.

In view of disaster looming, non-toxic, available and affordable drugs are urgently needed. But there is an obvious lack of research and development: of 1223 new molecules marketed between 1975 and 1997, only 11 were for tropical diseases. Absence of profitable markets is the main reason; patients are numerous but they are so poor that neither they nor their governments are able to pay, even for essential drugs. This situation raised serious concern and a number of yet unanswered questions. In response, WHO created a network of field researchers, operational agents, epidemiologists and scientists from the Swiss Tropical Institute, the Institute of Tropical Medicine in Antwerp, the Centers for Disease Control (CDC), Médecins Sans Frontières (MSF), Epicentre, WHO, Tropical Diseases Research (TDR), industrial consultants and others (WHO 1999). The stated mission of this network is to 'monitor drug resistance, find and recommend solutions for the treatment of sleeping sickness'. The objectives are to assess the effectiveness of current regimens, to collect and disseminate information on refractoriness to treatment, to ensure availability and affordability of existing drugs, to provide guidelines and promote research on the causes of treatment failures, drugs and treatments. The network consists of a steering committee, a secretariat and four technical working groups responsible for research, surveillance, drugs and information.

The objectives of the drug group, led jointly by MSF and WHO, are to secure and maintain production of anti-trypanosomiasis drugs. It is planned to centralize drug purchases, group the orders and dispatch them to requesting programmes through the MSF purchasing centre. A special fund to secure the market and to sustain drug production will be necessary. Another immediate

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objective is to ensure the production, commercialization and registration of eflornithine in Africa and Europe.

Since April 1999 the situation has slightly improved: Production of melarsoprol, suramin and nifurtimox seems to be secure, the donation of pentamidine vials was extended through 2000, and discussions for a new agreement should take place soon. WHO and MSF are trying to find alternative producers for eflornithine. The high cost of this drug is a major concern and technical procedures need to be set up to make this drug affordable.

### Research and development

Burri *et al.* (2000) recently established the viability of a shorter, 10-day regimen for melarsoprol treatment. Nifurtimox (Lampit<sup>R</sup>), a registered drug used for treating American trypanosomiasis or Chagas' disease, requires more research into its pharmacokinetics and bioavailability to define the treatment protocol for the second stage of HAT before it can be registered for prescription in endemic countries. Berenil is highly efficient in animals and should be tested for human trypanosomiasis. Some producers have shown interest, and it may be possible to get support from the European Orphan Drug Act. Megazol, a nitroimidazole drug, has only been tried on monkeys and produced very good results. It is under further investigation and will not be available for some years yet. Various drug

combinations are also being considered and some of them are under investigation.

### Conclusions

We hope that the network initiated by WHO will succeed in sustaining the manufacturing of HAT drugs and encourage the research and development of new ones. This is an emergency – we may not be able to treat patients soon due to the scarcity of existing drugs and the lack of new ones against this fatal disease.

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