

SLEEPING SICKNESS

or Human African Trypanosomiasis



Sleeping sickness, or human African trypanosomiasis (HAT), is a fatal parasitic disease that affects 36 countries in sub-Saharan Africa: 60 million people are at risk. Nearly eliminated in the 1960s, HAT has been making a comeback of epidemic proportions due to war, population movements and the collapse of health systems over the past two decades.

Photo: © Serge Sibert/COSMOS



A boy is being tested for sleeping sickness in a Ugandan village. Combating sleeping sickness requires mobile teams to track down potentially infected people. This work is backed up by laboratory testing, treatment with appropriate drugs, and close monitoring of patients. If there is no local clinic where patients can be hospitalised, MSF sets up special treatment centres where teams provide drugs, training and supervision of local staff.

The World Health Organization (WHO) estimates that about 300,000 people are currently infected with HAT and that over 60,000 people die from it every year, although many more infections and deaths go unreported. The drugs currently in use to treat HAT are old, toxic or difficult to use. A donation programme was agreed between WHO and pharmaceutical producers in 2001 securing the supply of existing medicines to treat HAT until 2006. But ensuring adequate resources for research and development for new medicines against this devastating

disease is vital if we are to effectively treat patients and control the disease in the future. ■

MSF and Sleeping Sickness

Médecins Sans Frontières (MSF) has been treating patients with sleeping sickness for nearly 20 years. MSF currently runs 17 sleeping sickness programmes in remote and often politically unstable parts of Angola, the Central African Republic, Democratic Republic of Congo, Congo Brazzaville, Uganda and Sudan. Since 1986 when it first opened a sleeping sickness

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programme in Uganda, MSF has screened hundreds of thousands of Africans and treated 30,000. Prevention efforts such as vector control are crucial in keeping sleeping sickness at bay. But from MSF's perspective, the greatest obstacle to fighting the disease is the lack of new, better diagnosis and drugs. MSF is working to improve access to and quality of care offered to people suffering from sleeping sickness. ■

Transmission and Symptoms

The parasite causing sleeping sickness is transmitted to humans through the bite of infected tsetse flies breeding in warm and humid areas. Inhabiting the vast savannah across sub-Saharan Africa, tsetse flies come into contact with man, cattle and wild animals, all acting as reservoirs for the parasites.

There are two different sub-species of the trypanosome parasite: *Trypanosoma brucei gambiense* and *T.b. rhodesiense*. The former causes chronic disease and the latter becomes fatal much faster, but both progress in stages – and both kill if not treated.

The first stage of sleeping sickness presents with non-specific symptoms such as fever and weakness. This stage is difficult to diagnose but relatively easy to treat. However, if no treatment is given, the parasite will invade the infected person's central nervous system and the second stage sets in. This can be as early as a few weeks or as late as several years after infection, but it is when serious neurological and psychiatric problems inevitably start manifesting themselves: the person becomes confused or violent and may have convulsions. Named after one of its most striking symptoms, sleeping sickness is characterised by an inability to sleep during the night but being overcome by sleep during the day. If left untreated, the disease inevitably leads to coma and death. ■

Diagnosis: No Accurate Method Available

Diagnosing sleeping sickness relies on detecting parasites in the person's blood or lymph nodes. If the initial diagnosis is positive, it is followed by a lumbar puncture, a painful and potentially dangerous manoeuvre needed to determine whether the disease has reached its second stage. This procedure is applied because the medicines used to treat second stage disease are very toxic and may have fatal secondary effects, so they should only be administered to people who really need them. Current diagnostic methods are invasive and difficult to use in resource-poor settings as obtaining accurate results requires highly skilled staff. ■

Current Treatments: Long, Toxic and Complicated to Use

“Melarsoprol is a terrible drug – you don't feel proud injecting it. It is caustic, it burns, and you don't know if you are going to save your patient or kill him”

MSF Doctor, Uganda.

■ Archaic

First stage sleeping sickness can be treated with two existing drugs that were both developed more than half a century ago. Pentamidine (introduced in 1940) is used against *T.b. gambiense* and is usually well tolerated, but must be injected in muscles. Suramin (used since the 1920s) is used against *T.b. rhodesiense*. It has severe side effects, and a treatment course takes five weeks to complete.

■ Options: Death by drug or death by disease?

However, most infected people only seek treatment when the disease has already advanced to the second stage. The most common treatment at this stage against both types of the parasite is melarsoprol. Introduced in 1949, melarsoprol is a derivative of arsenic. It is so toxic that it melts plastic syringes, is extremely painful when injected and ends up killing one in every twenty patients receiving it. Furthermore, melarsoprol is becoming less and less effective. In some areas of Africa, such as Omugo, Uganda or Ibba, South Sudan where MSF is running sleeping sickness programmes, the drug fails to cure up to 30% of patients.

■ Miracle drug

There is a safer, more recent alternative to melarsoprol, called eflornithine, a drug originally developed to treat cancer. Eflornithine's activity against sleeping sickness was discovered by accident, and its production for this purpose was interrupted repeatedly (see box). Its spectacular success at pulling people out of a coma led to it being nicknamed the “resurrection drug”. But even the “miracle drug” has its disadvantages: eflornithine must be administered by slow drip infusions repeated every six hours during 14 days, a complicated treatment schedule that impairs wider use of the drug in rural Africa. Although far less toxic than melarsoprol, eflornithine can cause adverse reactions. In addition, it only works against *T.b. gambiense*, and there is reason to believe parasites could develop resistance to it rapidly when it is used alone. Before the launch of a specific, time-bound donation programme (see box), eflornithine was marketed at prices definitely out of reach of people suffering from sleeping sickness.

■ Not authorized for HAT

Nifurtimox, an oral drug, was discovered in 1960 through veterinary research and developed to treat Chagas disease. While nifurtimox has been used to treat second stage sleeping sickness patients who

didn't respond to other treatments, it is currently not registered for use against HAT. There is an urgent need to demonstrate the safety and efficacy of nifurtimox for this use. ■

Hairy business: Eflornithine's long road back to where it saves lives

Used to treat a neglected disease, eflornithine was never a profitable product. Hoechst Marion Roussel, the manufacturer at the time, ceased production in 1995, only five years after the drug had first reached the market. In early 2000 stock was running dangerously low, and WHO began searching for a long-term solution with the help of MSF. 12 candidates were investigated in order to find a producer who would agree to continue manufacturing eflornithine. Meanwhile, in late 2000, Bristol-Myers Squibb was running six-page ads and TV commercials to market Vaniqa, an eflornithine-based women's facial hair remover, across the developed world.

There is little doubt that the media attention sparked by the Vaniqa launch accelerated eflornithine's subsequent return in the sleeping sickness medicine cabinet. In May 2001, Aventis and WHO signed a deal ensuring the production of eflornithine and two other sleeping sickness medicines, melarsoprol and pentamidine. The donation covers global need until 2006. The total value of the donation is US\$ 5 million per year as the agreement also included funding for WHO's programmes for sleeping sickness treatment and research over five years; in addition, Aventis agreed to transfer technology and provide technical assistance to potential long-term manufacturers of the drugs. Bayer had announced that it would restart the production of two other sleeping sickness drugs, nifurtimox and suramin, in 2000.

In addition to actively working to maintain a steady supply of these medicines, MSF shares responsibility of distributing them to sleeping sickness programmes in central and southern Africa. Based on orders sent to WHO, WHO and MSF dispatch the drugs to programmes run by national governments or agencies like MSF, IMC, Malteser and CARE.

As one of the main users of the drugs included in the donation programme, MSF is keen to ensure that there is a continuous supply of existing sleeping sickness drugs until new drugs can be introduced. In a May 2004 communications to MSF, Aventis assured that by early 2006 at the latest, "industrial capacities to produce eflornithine, pentamidine and melarsoprol will be either maintained within Aventis (or its successor Sanofi-Aventis) or transferred to other producers" while ensuring that quality, long-term commitment to production and "affordable economic conditions" remain unchanged.

Replenishing the Drug Development Pipeline: A Public Sector Responsibility

Sleeping sickness is a classic example of a neglected disease: only poor people in remote areas suffer from it, so there is no profit potential in developing drugs to combat it. That is why, apart from eflornithine, there has been no significant improvement in HAT treatment for 50 years.

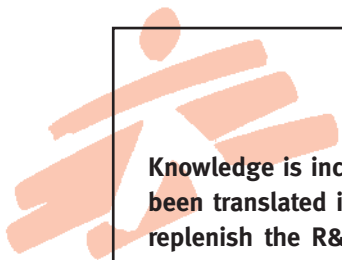
This is beginning to change. A consortium of research groups led by the University of North Carolina at Chapel Hill and funded by the Bill and

Melinda Gates Foundation is exploring a series of pentamidine derivatives. The most advanced compound, called DB 289, is in Phase II clinical testing and the results so far are promising; but even if this compound is successfully completed, it will only be active against first stage HAT.

In 2003, MSF co-founded and launched an independent not-for-profit drug development organisation, the Drugs for Neglected Diseases initiative comprising MSF, the WHO Special

Programme for Research and Training in Tropical Diseases (TDR), the Oswaldo Cruz Foundation/Fiocruz (Brazil), the Indian Council of Medical Research, Institut Pasteur (France), the Malaysian Ministry of Health and the Kenyan Medical Research Institute. With an initial focus on sleeping sickness, visceral leishmaniasis and Chagas disease, DNDi has begun several discovery

projects aiming to identify novel lead compounds. Firmly rooted in needs identified by MSF and others providing care to patients in endemic countries, DNDi is also working on projects with shorter-term objectives, such as developing a treatment using nifurtimox and eflornithine to replace melarsoprol or eflornithine in monotherapy, a project developed in cooperation with WHO/TDR. ■

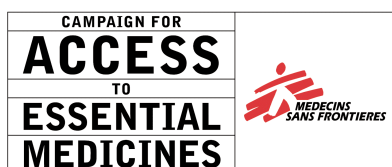


Knowledge is increasing about sleeping sickness and the parasites causing it, but this has so far not been translated into new diagnosis and drugs to tackle the disease. A worldwide boost is needed to replenish the R&D pipeline. Scientific knowledge and technological progress must be harnessed to design, develop and implement improved treatment options to those who need them.

A needs-driven, priority R&D agenda for sleeping sickness must be developed and properly resourced as a matter of urgency. From MSF's perspective, the following are top priorities:

- New, easy-to-use and accurate diagnostic tests including ability to determine the stage of the disease.
- Ensuring the production and supply of existing sleeping sickness drugs.
- Developing new treatment protocols using combinations of existing drugs to avoid drug resistance.
- New, easy-to-use drugs, including ones that can be taken orally.
- Ensuring the affordability of all the above.

MSF is confronted with the lack of appropriate diagnostic tests and drugs to tackle diseases of the poor in its field activities every day. This is why MSF is advocating for political commitment by WHO, the international community and governments of endemic and wealthy countries to support existing and new initiatives developing new tools to combat neglected diseases.



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