CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

Human African Trypanosomiasis

Facing the challenges caused by neglect:

The need for new treatment and diagnostics

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Preface

This document provides an overview of the current issues surrounding the control of human African trypanosomiasis (HAT), better known as sleeping sickness, caused by the parasite *Trypanosoma brucei gambiense*. It is meant for both medical and non-medical readers, and presents overall global trends as well as MSF's perspective on the current situation.

The information presented here is not intended to replace or amend either current World Health Organization recommendations on HAT management or MSF's own HAT manual. Similarly, it should not be considered to be an exhaustive opinion on the global epidemiology of HAT or issues surrounding diagnostic and therapeutic approaches. Nor is it a comprehensive literature review, although references are provided to guide readers towards more in-depth sources of information.

We hope that this document will facilitate efforts to guarantee future availability of effective HAT diagnostic tests and treatments, and encourage MSF and others to continue their crucial work against HAT, one of the world's most neglected tropical diseases.

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Authors

Francesco Checchi
Graciela Diap
Unni Karunakara

Médecins Sans Frontières
Campaign for Access to Essential Medicines

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Nathan Ford (Médecins Sans Frontières)

Lisa Hayes, editorial assistance

Médecins Sans Frontières (MSF) is an international humanitarian aid organisation that provides emergency medical assistance to populations in danger in more than 80 countries. As a medical humanitarian organisation, it is fundamentally unacceptable to MSF that access to essential medicines is increasingly difficult, particularly for the most common infectious diseases affecting poor countries. Since 1999, MSF has been campaigning internationally to find long-term, sustainable solutions to this crisis. The Campaign for Access to Essential Medicines is pushing to lower the prices of existing medicines, to bring abandoned drugs back into production, to stimulate research and development for diseases that primarily affect the poor, and to overcome other barriers to access.

For more information about the campaign, visit: http://www.accessmed-msf.org

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Summary

Each year more than 50,000 people become infected with human African trypanosomiasis (HAT), commonly known as sleeping sickness. This parasitic disease transmitted by the tsetse fly mostly affects people living in poor countries within sub-Saharan Africa. The disease progresses from an asymptomatic or mild phase to an increasingly severe terminal phase leading to behavioural changes, sleep alterations, immunological and organ malfunctions, severe wasting, and eventually irreversible coma and death. If patients are able to get the needed medical care, they face a painful diagnostic process and treatment. Those who have no access to screening or treatment will die.

HAT has experienced a resurgence since the end of the colonial period in Africa. Since the era of independence in the 1960s, many African countries have had inadequate health budgets to continue routine control activities. Most have also lacked the political will to tackle this key health problem. The fall in the number of people screened for sleeping sickness and the corresponding increase in HAT cases in Africa starting in the 1970s resulted in alarming HAT epidemics in the 1990s.

While more and more is understood about the parasite, too little is being done to find more effective diagnostic tools and less toxic treatments for its sufferers. Drug development for HAT stopped in 1949 and no new medicines have appeared since the early 1990s. Case detection and diagnosis remain unsatisfactory, due to the insufficient accuracy of available tests. Treatment is also problematic, taking place over several days due to the complexity of available drug regimens – administered by injection or infusion – and therefore requiring significant nursing capacity. In addition, it is now clear that the historical mainstay of first-line treatment for advanced cases, the drug melarsoprol, (an arsenic derivative) is extremely toxic and an increasingly ineffective therapy.

In 1986 teams from Médecins Sans Frontières (MSF) first provided care to people affected by a HAT epidemic in Uganda. By December 2005, MSF programmes had screened at least 2,400,000 people and treated approximately 43,000, the majority of whom were already suffering from the disease's advanced stage (stage 2). Today MSF remains a major provider of sleeping sickness treatment with programmes in all of the significantly affected countries. MSF's share of the total caseload was 18% (3,075/17,036) in 2004. It is currently solely responsible for the efficient supply and distribution of all HAT drugs used in the world today.

Despite these impressive numbers, MSF, national treatment programmes, and other organisations involved in HAT treatment have become increasingly confronted with difficulties in diagnosing and treating people with HAT. Currently treatment of people infected with this parasitic disease relies on a remarkably limited drug arsenal. Eflornithine, while promoted by MSF as a more effective and safer first-line treatment for patients in stage 2 is more expensive for patients and more difficult to administer. Its use calls for more sophisticated health facilities and trained health staff, both an ongoing scarcity in many areas where the disease is endemic.

Much more needs to be done to promote the use of existing drugs, including eflornithine and its potential new combination partner, nifurtimox. There is an urgent need for larger amounts of eflornithine to be used in the field in order to replace the older, more toxic drug melarsoprol. This can only happen if the capacity of health care providers is increased and the necessary materials needed to administer eflornithine are provided for free. Making eflornithine and nifurtimox more readily available to treatment programmes will encourage their use and stimulate innovation. Combination therapy with eflornithine and nifurtimox has clear advantages over currently used monotherapies and its use in the field should be expedited by completing the necessary studies, especially as it is currently believed to be the best option available to treat people in stage 2 until new drugs are developed.

However, due to the lack of a profitable market, HAT drugs hold little interest for the world's pharmaceutical industry. Most HAT drugs had been taken out of production until MSF and others launched international campaigns to make the drugs available again. Today a number of producers, working with the World Health Organization (WHO), have promised to guarantee a free supply of the needed drugs in the form of drug donations. While

providing a short-term solution, this complete dependence on time-limited drug donations is unsustainable and dangerous.

The price for neglecting HAT control is high and paid for in the form of dramatic, lethal epidemics which are often detected too late. Without political understanding and awareness of the consequences of interrupting control, funding for HAT programmes may soon evaporate, and there is a clear danger that the epidemic wave of the 1990s will be repeated.

There is an increasing realisation that new operational models are needed for HAT treatment and control efforts to be sustainable. With downward trends in prevalence, it is time to move away from expensive vertical programmes to cheaper, integrated health care at peripheral levels. For this to happen, new diagnostic tools and treatments are needed. There is now a revival of HAT research and development compared to 15 years ago. However, most of the research into new drugs to treat HAT patients is in the earliest stages of the development process. The greatest therapeutic need in HAT – safe, efficacious and affordable drugs to treat patients in stage 2 of the disease – remains a distant goal. Although it is possible that a new drug will be available within the next decade, there remains a strong case for further acceleration and expansion of drug development efforts.

MSF recommends three main actions to promote better diagnostics and treatment for sleeping sickness patients:

- Patients need the most effective therapy. For that reason, eflornithine-based treatments must become more accessible to patients as quickly as possible. For this to happen, eflornithine use must be promoted at both the international and national level. There is an urgent need to build capacity within national treatment programmes to administer eflornithine and to provide free infusion kits to increase access to effective therapies.

- Because the future of the drug nifurtimox is insecure at present, the WHO should conduct vigorous discussions with pharmaceutical firm Bayer to ensure easy access to the drug and its continued availability for use in HAT treatment programmes.

- To ensure needs-based research and development, the public sector, including national governments strongly affected by the disease, needs to become more actively involved in setting priorities for research and development as well as resource allocation for neglected diseases research. In addition, the wider research community should find ways to accelerate research on new molecules, therapies and diagnostics that will lead to easy and safe detection, staging and treatment of those with the disease.

1. Background

1.1 Introduction

Human African trypanosomiasis (HAT), commonly known as sleeping sickness, is one of the world's most neglected parasitic diseases, each year affecting about 50,000 to 70,000 people living in sub-Saharan Africa[1]. This World Health Organization (WHO) figure is a rough estimate based on reported annual incidences, for instance, 17,500 for the year 2005. Most of the disease burden is shared by a few highly endemic countries: the Democratic Republic of Congo (DRC), Angola, southern Sudan, the Republic of Congo (RoC), the Central African Republic (CAR), and Uganda. Two forms of the disease are known: an acute illness, lasting on average two months, caused by the parasite sub-species *Trypanosoma brucei rhodesiense*; and a more chronic illness, lasting two years or more, for which *Trypanosoma brucei gambiense* is responsible. Both forms are transmitted through the bite of infected tsetse (*Glossina spp.*) flies. *T. b. rhodesiense HAT* is primarily a disease found among cattle, and humans are only accidentally infected. This disease occurs in several foci in eastern and southern Africa.
T. b. gambiense HAT essentially affects humans, and foci (about 200) are found west of the Rift Valley. Throughout this report, the acronym HAT is used to signify the *T. b. gambiense* form of the disease, which currently causes the vast majority of sleeping sickness cases and deaths among humans in Africa.

HAT is fatal if left untreated. Terminal HAT illness is extremely painful for both patients and their families. The disease progresses from an asymptomatic or mild phase (stage 1, lasting several months to years) to an increasingly severe terminal phase (stage 2, which lasts a few years). In stage 1, parasites reproduce in the blood and lymphatic system of the person. In stage 2 they cross the blood-brain barrier, leading to behavioural changes, sleep alterations, immunological and organ malfunctions, severe wasting, and eventually irreversible coma and death.

How HAT transmission takes place

Depending on their species, tsetse flies breed in rainforests or more commonly near streams and bodies of water. Adult flies have a lifespan of approximately two months. Although tsetse fly populations are affected by weather and changes in land use, fly populations alone are not predictive of the rate of infection. The dynamics of fly-human transmission are complex and not yet fully understood, although it is agreed that they depend to a great extent on:

tsetse fly feeding preferences – in the presence of certain species of wild game (e.g. antelopes) or domestic animals (e.g. pigs and cattle), flies may rely less on humans for their blood meals, resulting in lower incidence.

frequency of human-fly contact – most infections occur near the breeding sites of the fly in savannah regions, contact is particularly intense in the dry season when both flies and human beings rely on the same scarce water sources.

Flies contract the infection from humans with HAT, essentially only during their first bite, but they then remain infectious to other humans for their entire lifespan, provided that they can survive a minimal period of approximately 18 days after the initial bite (the time it takes for the parasite to complete its life cycle inside the fly).

Main options to control HAT

TThe immediate goal of all HAT treatment programmes is to save the lives of infected patients through accurate diagnosis and effective treatment. In addition, in order to control disease transmission in the community, two complementary approaches are possible:

- **reduction in the number and life expectancy of tsetse flies** so as to minimise fly-human contact and interrupt the fly-human-fly transmission cycle;
- **treatment of as many infected people as possible,** in order to reduce the reservoir of infectious individuals (prevalence).

Tsetse fly control programmes, essentially relying on simple trapping devices, can play an important role, especially when HAT prevalence is high. However, **finding and treating cases is by far the most important control measure**. Passively detecting cases† at HAT

† Screening efforts can be active or passive. Passive screening occurs once patients present at a health facility in search of care for illness. Active screening calls for medical personnel to visit local communities and test many individuals in the area for the disease.

Box 1: The importance of active case finding in controlling HAT

- Maximises treatment coverage
- Detects the majority of cases early (stage 1)
  - Stage 1 cases are easier to treat, have a better chance of being cured, and experience fewer side effects than stage 2 cases
  - Cases detected early also remain infectious for a shorter period
- Dramatically and rapidly reduces the infectious reservoir and hence transmission settings where most of the patients are seen

treatment centres is simply not enough: stage 1 cases are less likely to present themselves for treatment, as the distance people must travel to reach a health facility is an obstacle in nearly all active HAT foci[2]. Active case-finding campaigns are therefore necessary, demanding that teams travel to isolated communities and attempt to screen the entire population (Box 1).

Suspected cases are then referred to specialised inpatient HAT treatment centres where the diagnosis can be confirmed, the clinical stage determined, and treatment administered. After discharge, patients should return for routine visits over the following two years so as to ensure that the treatment has been effective. Whether this happens in practice depends on the quality and capacity of treatment programmes.

Case detection and diagnosis is always less than perfect, due to the insufficient accuracy of available tests. Treatment is also problematic, taking place over several days due to the complexity of the available drug regimens – administration is either by injection or infusion, requiring significant nursing capacity. Stage 2 patients are often severely ill and require a comprehensive package of medical care. (Details of diagnosis and treatment constraints are provided in Sections 1.3. and 2.3.)

HAT control requires a lasting, adequate supply of accurate diagnostic tools and effective drugs. Currently, patients are diagnosed and staged in difficult settings where the disease is commonly found, including isolated communities, hard-to-reach terrain and conflict areas. In addition, the drugs now being used to treat patients with sleeping sickness are antiquated and there is not enough research and development underway that will ensure new, effective treatments within the next decade.

1.2 The last two decades

HAT's dramatic comeback and MSF's response

HAT's spread through the African continent is largely attributable to environmental and social upheavals brought about by colonial policies. Between the start of the 20th century and the end of World War II, dramatic HAT epidemics raged in the Congo basin (an estimated 500,000 deaths), Uganda (200,000 deaths), Sudan, Angola, Cameroon, Nigeria, Guinea, Liberia and Sierra Leone[3]. **Millions died; millions more had no choice but to migrate away from fly-infested areas. Entire human settlements ceased to exist.** These emergencies prompted colonial administrators to establish the first vertical HAT control programmes, which, through a combination of active screening of affected populations, treatment, mass chemoprophylaxis, and more coercive measures such as quarantine and forced relocation of communities, managed to bring the disease under control to such an extent that by the early 1960s HAT appeared to be on the verge of elimination in most active foci.

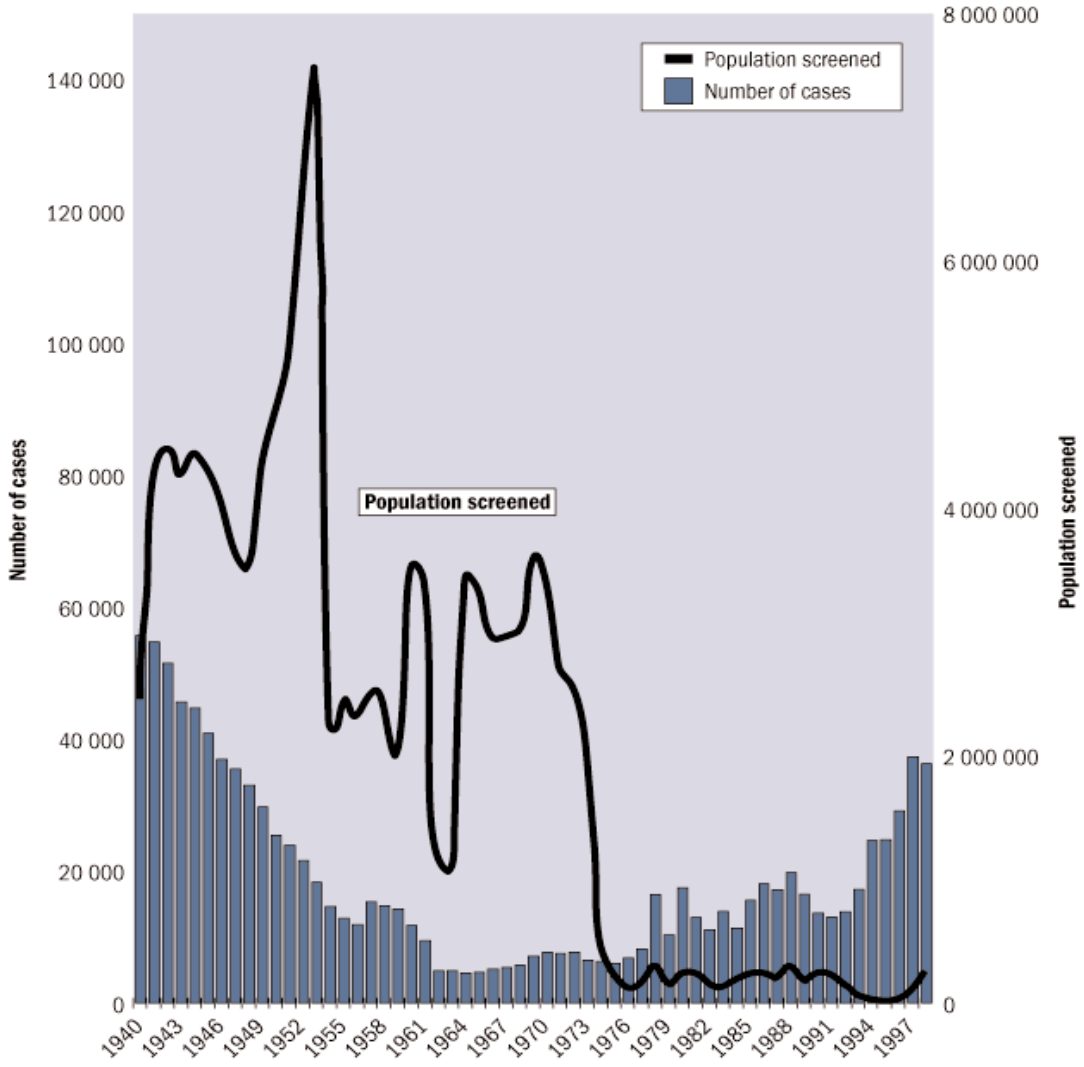
Post-decolonisation neglect

The resurgence of HAT after the end of colonialism represents an example of international neglect in disease control and tropical disease research that is difficult to beat.[4] After gaining independence, many HAT-endemic African countries had inadequate budgets to continue routine control activities and lacked the political will to tackle key public health priorities. Armed conflict also erupted in all historically large HAT foci (Uganda, southern Sudan, RoC, Zaire, and Angola), almost completely halting active screening and vector control activities. The fall in the number of people under screening surveillance, and the corresponding resurgence of HAT in Africa starting in the 1970s resulted in alarming epidemics in the 1990s (Figure 1). This pattern is evident in all of central Africa. For

example in Angola[5] only three new cases were detected countrywide in 1974, compared to 6,610 in 1998. **The bulk of the epidemics in the 1990s may well have gone unrecorded in remote or war-affected areas of the Congos, southern Sudan, and Angola, where case detection was not available.**

Just as HAT became neglected in the endemic countries, so did research on its diagnosis and treatment. Drug development for HAT stopped in 1949 and no new medicines appeared until the early 1990s.

Figure 1. Annual trends in reported HAT cases and the number of persons screened for the disease in Africa (1940-1997)



Source: *WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases* (http://www.who.int/emcdocuments/surveillance/docs/whocdscsrisr2001.html; accessed 02/04/2005)

MSF gets involved

MSF teams were first confronted with a HAT epidemic in Uganda's West Nile region in 1986,[6] where HAT prevalence as high as 8% was initially recorded among Sudanese and Ugandan displaced populations. Over 15 years, MSF's programmes screened 981,939 people, and treated 18,132. By 2002, prevalence had been brought down significantly throughout the region, and the annual incidence was only 6 cases per 10,000 inhabitants[7].

Other MSF HAT programmes followed in southern Sudan, Angola, DRC, RoC, and CAR (see Table 1).

As of December 2005, MSF programmes had screened at least 2,400,000 persons (data from Angola and DRC are incomplete), **and treated approximately 43,000 patients, of whom 64% were in stage 2.**

Despite these impressive numbers, MSF teams have been confronted with difficulties in diagnosing and treating HAT cases. It has become increasingly apparent that the historical mainstay of first-line, stage 2 treatment, the drug melarsoprol, is extremely toxic and increasingly ineffective in a growing number of foci.

Table 1. MSF HAT programmes by focus, section, period of activity, and outcomes

Country	Focus	Section	Period	Status	Screened	Treated
Uganda	Moyo	France	1986-1993	handed over	399,311	8,804
	Adjumani	France	1991-1996	handed over	286,120	5,697
	Omugo	France	1995-2002	handed over	289,686	3,460
	Yumbe	France	2000-2002	handed over	11,032	208
Southern Sudan	Ibba	Holland	1999-2000	handed over to MSF-France	17,706	1,081
	Ibba, Kotobi, Maridi	France	2000-present	ongoing	146,836	4,495
	Kiri, Kajo Keji	Switzerland	2000-present	ongoing	152,937	2,877
	Tambura	Spain	2005-present	ongoing	32,930	493
Central African Republic	Haut Mboumou	Spain	2001-present	ongoing	60,171	2,172
Republic of Congo	Plateaux	Holland	2000-2003	handed over	58,417	913
	Bouenza	Holland	2001-2005	closed	212,214	1,238
	Cuvette Est	Holland	2002-2005	closed	42,628	616
	Pool, Ngabe	Holland	2005-present	ongoing	23,889	129
Democratic Republic of Congo	Equateur Sud	Belgium	1998-2002	handed over	300,017	665
	Isangi, Province Orientale	Belgium	2004-present	ongoing	62,398	927
	Equateur Nord	France	2004-2005	closed	›4,624	154
Angola	Ndalatando, Kwanza Norte	Belgium	1995-2001	handed over	216,309	7,584
	Caxito, Bengo	Belgium	2002-2003	ongoing	83,375	1,205
	Camabatela, Kwanza Norte	France	2004-present	closing	›8,300	200
TOTAL	19 programmes (7 ongoing)				›2,408,900	42,908

Source: MSF HAT working group, figures as of end 2005

1.3 A drug crisis

The dire lack of therapeutic options

To date, treatment of people with HAT relies on a remarkably limited drug arsenal. **Only one drug, pentamidine, is available to cure stage 1 of the *gambiense* disease** (suramin is used for *rhodesiense* cases). Two drugs are registered for treatment of people in stage 2-melarsoprol and eflornithine-and another, nifurtimox (developed for Chagas disease), is used on a compassionate basis†† despite not being registered for use in sleeping sickness. The key features of these drugs are presented in Table 2.

Table 2. Description of drugs available to treat *T. b. gambiense* HAT

	Pentamidine isethionate	Melarsoprol (Arsobal®)	Eflornithine (Ornidyl®)	Nifurtimox (Lampit®)
Indication	stage 1	stage 2 (first-line)	stage 2 (second-line, increasingly used as first-line due to melarsoprol's toxicity and a growing level of resistance to it)	stage 2 (second-line, mostly used in combination)
Mode of administration	intramuscular injection	intravenous injection	intravenous infusion	oral
Typical regimen	daily for 7-10 days	historical standard: three injections a day for 3 days, repeated 3 times, with a 7-day rest period in between the series New recommendation: 10-day short regimen	four infusions per day for 14 days (first-line) or 7 days (second-line)	three times a day for 14 days
Relapse rate	low (<10%) despite widespread past use with sub-standard doses	increasing (up to 35% depending on the site)	10-15% at 24 months in MSF programmes	high (up to 37%) if given as monotherapy
Side effects	mild, non-fatal	many and severe: reactive encephalopathy in 5-10% of patients (50% fatal)	frequent but non-fatal and reversible if treatment is stopped	poorly documented: generally low, but increasingly severe with duration of treatment
Present manufacturer	sanofi-aventis	sanofi-aventis	sanofi-aventis	Bayer AG
Price of full treatment course in US$ (year) prior to donation agreements	20-25 (pre-2000, already given at cost-recovery level)	54-80 (pre-2001)	~700 (1999)	10-15 (2002)

The toxicity of melarsoprol, an arsenic derivative introduced in 1949, makes stage 2 treatment both very painful and highly toxic, causing death in approximately 5% of the patients treated with it. Staging of the disease is equally difficult as it can only be done using a lumbar puncture. Largely in order to minimise the risk of patients being misclassified as stage 2 and treated with melarosprol, HAT diagnosis has come to rely on very complex algorithms (see Figure 8). The already dire situation has worsened since the 1980s when increasing treatment failure rates for melarsoprol were noted by MSF teams[8]. Today, high melarsoprol failure rates have been reported in several foci in Uganda (31%), southern Sudan (18%), and Angola (25%)[9].

The increasing phenomenon of melarsoprol treatment failure has led to the use, on a compassionate basis, of other drug regimens that have not been formally validated, such as nifurtimox alone or various combinations of melarsoprol, eflornithine and nifurtimox (see Table 2).

†† The drug is used on a compassionate basis in advanced patients when approved treatment options have been exhausted.

The rise of eflornithine

The trypanostatic properties of eflornithine, or difluoromethyl-ornithine (DFMO), initially developed as an anti-cancer drug, were first noted in 1980[10]. When used on a compassionate basis among stage 2 HAT cases, the drug immediately made an impression on clinicians due to its far lower toxicity compared to melarsoprol, as well as its rapid action. For these reasons, it was christened the "resurrection drug". Small but conclusive safety and efficacy trials followed, and the drug was registered for use in people with stage 2 HAT in 1990, in what was the first major breakthrough in HAT treatment research in 50 years[11]. Nevertheless, the use of eflornithine since then has been limited by two factors:

- **Very high cost per treatment** (around US$ 700) before the one-off 1999 and the negotiated 2001 WHO-Aventis donation agreements.
- **Extremely difficult administration**: the drug must be given 4 times a day in 2-hourly infusions over 14 days. This requires inpatient facilities, around the clock nursing care, precautions to avoid bacterial infections and relatively sophisticated and costly materials (infusion fluids, needles, and catheters).

Drug production grinds to a halt

Throughout the 1990s, production of stage 2 drugs was haphazard at best. Despite increasing scientific evidence in favour of the drug's use in HAT, the manufacturer, Hoechst Marion Roussel, renamed Aventis Pharma and now known as sanofi-aventis, stopped producing eflornithine altogether in 1995, citing its lack of profitability. Pressure from WHO and MSF led the manufacturer to release a small overlooked stock in 1998, and to produce an additional 10,000 vials in 1999. By 2000, however, supplies were again running dangerously low.

To make matters worse, Bayer, the maker of nifurtimox, indicated that it was planning to stop production just as the drug became increasingly important in the field as a last resort for melarsoprol-resistant relapses. In 1997, Bayer discontinued production of nifurtimox. To secure supplies for HAT patients, MSF immediately purchased the last remaining stock (500,000 tablets, or approximately 10-15,000 treatments) from Bayer's Argentinian production unit. At the same time, Bayer also discontinued production of suramin (Germanin®), the only drug available to treat stage 1 of r*hodesiense* HAT.

1.4 A way forward

Bayer restarts nifurtimox and suramin production

Thanks in good part to advocacy efforts by MSF and its newly founded Campaign for Access to Essential Medicines, Bayer announced in 1999 that it would resume production of both nifurtimox and suramin. At the time of writing, a donation of nifurtimox from Bayer for two years, is being negotiated by WHO for use in treating people with Chagas disease. In the future, the company anticipates offering the drug to WHO at a "preferred price"[12]. A separate WHO-Bayer agreement covers a five-year initial donation of suramin.

Bayer is also nominally supporting research to strengthen the evidence base on the safety, efficacy and dosing of nifurtimox for use in HAT, as part of a recently negotiated (2004) Bayer-UNICEF-UNDP-World Bank-WHO Special Programme for Research & Training in Tropical Diseases (TDR) Clinical Trials Material Supply Agreement by making available 200,000 tablets (representing approximately 2,000-3,000 treatments) for research purposes. The objective is to enable WHO to issue a formal recommendation on the drug's use either on a compassionate basis or as part of an eflornithine-based combination regimen. This legal starting point (which is not equivalent to a donation) also enables **limited compassionate use of nifurtimox for therapeutic purposes**. At the time of writing, this is a **"Named Patient Programme"**, requiring detailed monitoring and documentation on each patient treated with nifurtimox on a compassionate basis in order to generate further data on safety and efficacy. National programmes wishing to use nifurtimox must send an official request to WHO via their respective Ministry of Health, which must agree to accept liability in case of drug-related adverse events. However, to date, WHO's and Bayer's strong insistence on having countries assume full legal responsibility for the drug's use is hampering innovations in therapy.

WHO and Aventis agreement on nifurtimox, melarsoprol and eflornithine

Just as Aventis Pharma's eflornithine production faltered, another company, Bristol-Myers Squibb, launched a facial-hair-removal product (Vaniqa®) based on eflornithine, in October 2000. The stark contrast between eflornithine production for cosmetic use in the North and its appalling scarcity for treating a fatal African disease provided the basis for a strong

MSF campaign that led to an agreement in May 2001 between WHO and Aventis (involving Bristol-Myers Squibb) to continue production and supply of the drug.

As part of a previous licensing agreement (1999), Aventis had already agreed to hand over license rights and manufacturing expertise to WHO, with the objective of finding a new manufacturer for eflornithine[13]. The 2001 agreement, however, secured a mid-term supply of HAT drugs, by providing for the following:[14]

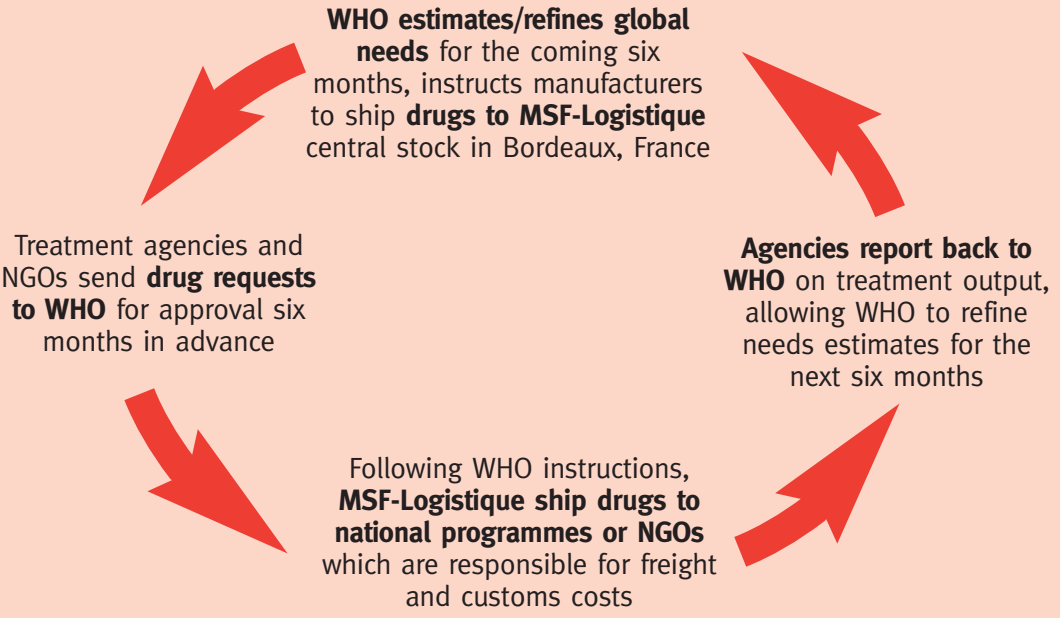
- Aventis guaranteed a five-year free supply of pentamidine, melarsoprol and eflornithine, representing a total value of US$ 12.5 million.
- Bristol-Myers Squibb donated raw material for the manufacture of 60,000 eflornithine vials (roughly one year's supply).
- Aventis committed a further US$12.5 million towards strengthening WHO's HAT management and control activities (including training, support to national programmes, and surveillance), as well as research and development on improved or new HAT drugs.

MSF was instrumental in the negotiation of this agreement, and continues to provide much of its logistical support. Requests for HAT drugs are sent to WHO. Once approved, sanofi-aventis and Bayer ship drugs to MSF's logistics centre in Bordeaux, France. From there, supplies are sent out to all recipient agencies (see Box 2).

In the past few years, sanofi-aventis has managed to secure the availability of raw materials and production of eflornithine. Eflornithine is now produced by Scinopharm in Taiwan.

The 2001 agreement expired in May 2006 and WHO and sanofi-aventis have now negotiated an extension of the contract for another five years. One of the key objectives for the coming years will be to increase the use of eflornithine by national treatment programmes. It is also expected that the new donation will include provisions to provide free infusion kits to facilitate the use of eflornithine and will primarily target selected national programmes.

Box 2: Mechanism of the WHO-Aventis-Bayer agreements

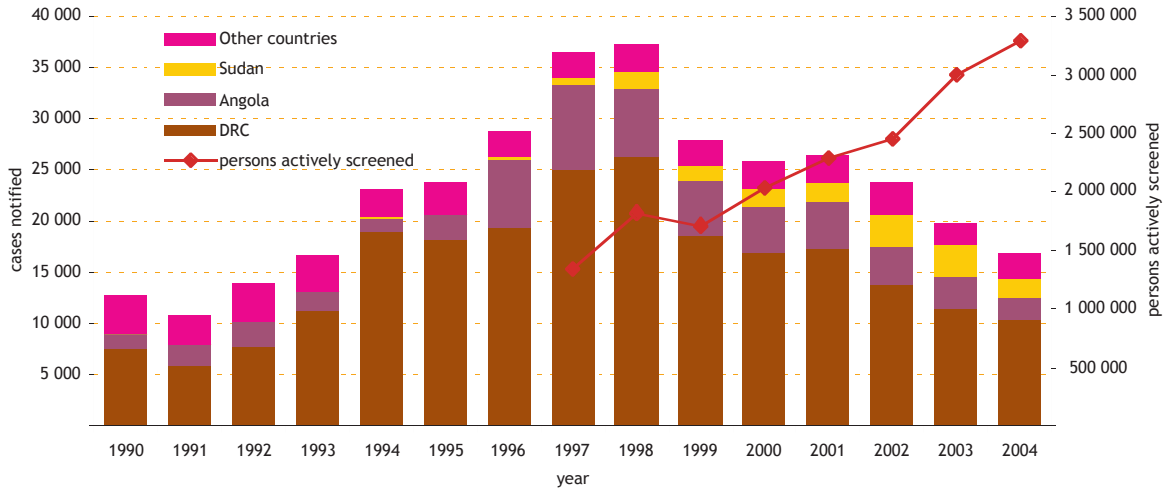


2. Overview of the current disease situation

2.1 Latest trends in HAT epidemiology

Worldwide, WHO was notified about **17,036 *T. b. gambiense* cases in 2004** (of which 10,369 or 60.9% occurred in DRC, in Angola, 1,766 in southern Sudan, 859 in RoC, 737 in CAR, and 354 in Uganda). This is a significant reduction from a peak in 1998 (37,385 cases), and is comparable to 1993 levels (16,607 cases). *T. b. rhodesiense* cases were far fewer (580). A progressive decrease in caseload has been noted in the past five years, although case-finding activities have increased, with more than three million people actively screened per year in 2003 and 2004 (see Figure 2).

Figure 2. Annual trends in number of *T. b. gambiense* cases notified throughout Africa, and total number of persons actively screened, 1990-20041



Help arrives in the most affected countries

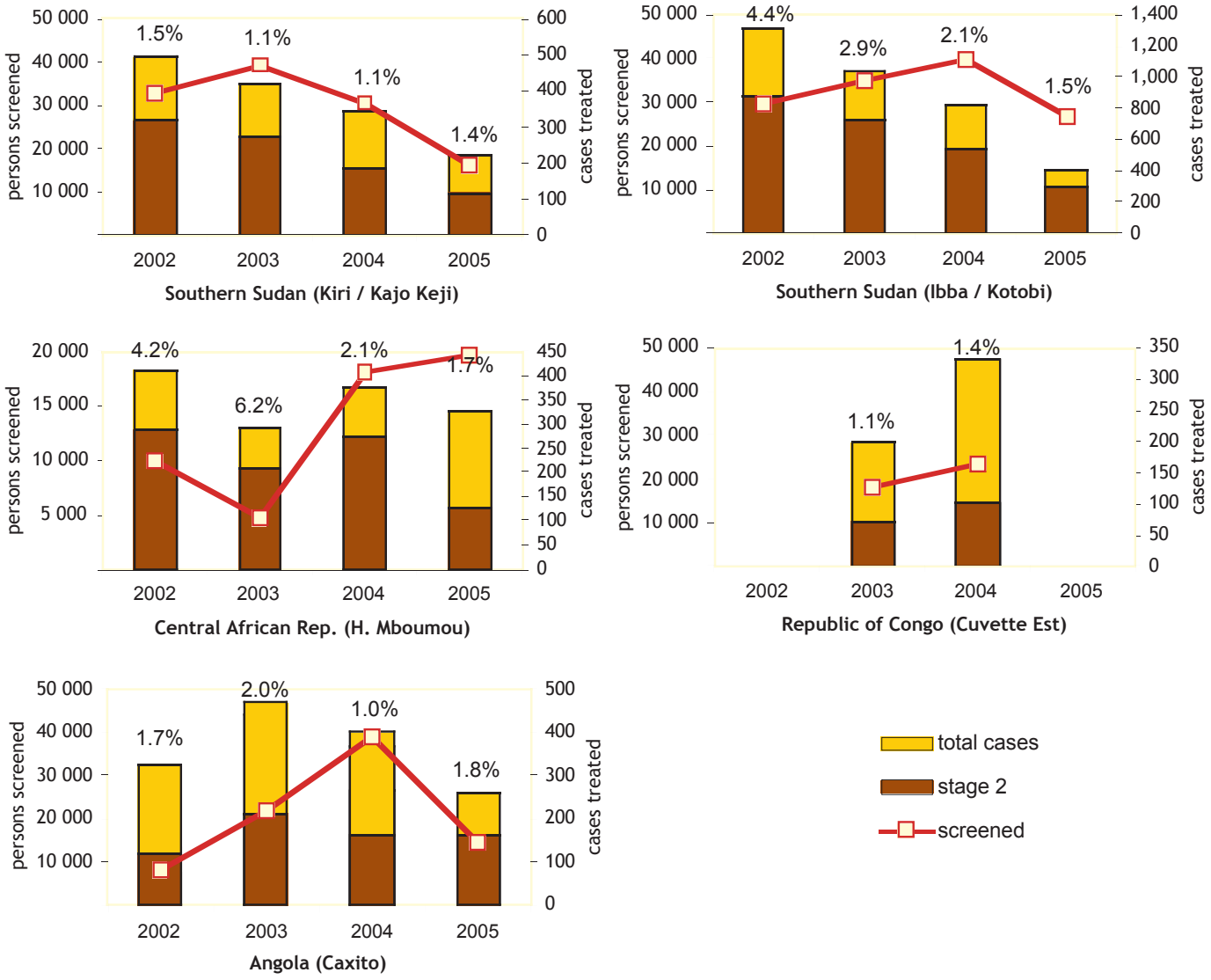
Table 3. Overall MSF HAT treatment output, 2003-2005
(Totals include small numbers of serological suspects who received presumptive treatment, and are thus slightly higher than the sum of stage 1 and stage 2 cases.)

	2003		2004		2005	
	n	%	N	%	n	%
Total # screened	187,721		297,000		196,746	
Stage 1 treated	1,102	38.1	1,260	41.0	1,455	52.0
Stage 2 treated	1,724	59.5	1,782	58.0	1,227	43.9
Total treated	**2,896**		**3,075**		**2,796**	

Source: MSF HAT working group

Since the early 1990s, non-governmental organisations (NGOs) have increasingly played a dominant role in HAT control, substituting for or supporting under-resourced national programmes. MSF, the International Medical Corps, CARE and Malteser (southern Sudan)[15], Caritas/Angotrip (Angola)[16], FOMETRO and MEMISA (DRC) have all initiated sizeable HAT programmes. Donor interest, notably from the French and Belgian governments, has also increased, allowing for wide-scale resumption of HAT control programmes by the Ministry of Health in the DRC.[17] **MSF remains a major treatment provider for *gambiense* cases, with programmes in all of the significantly affected countries. MSF's share of total caseload was 15% (2,896/19,901) in 2003 and 18% (3,075/17,036) in 2004.** In addition to screening and treatment, MSF has implemented vector control measures in Angola (Caxito) and RoC (Gamboma).

Figure 3. Trends in number of cases treated (by stage) and number of persons screened in seven MSF HAT programmes (2002-2005)
(Percentages indicate crude prevalence, calculated as cases/persons screened. Note that the extent of active vs. passive screening influences the crude prevalence measure. Crude prevalence figures are thus merely indicative of broad trends.)



Source: MSF HAT working group

MSF data collected from programmes consistently active between 2002 and 2005 show a roughly steady level of screening activities, and a stationary or downward trend in HAT caseload (Figure 3). Overall, screening and the numbers of cases treated by MSF have remained stable over the past three years (Table 3), but stage 1 patients became a majority in 2005. Improved political stability has enabled all actors to gain greater access to HAT foci.

Table 4. Screening output and coverage in five highly HAT endemic countries in 2004

Treatment output (focus/region)	Major foci/regions (treatment agencies active)
Angola (2.8 million at risk) Total: 356,242 screened; 2,280 cases (prevalence 0.6%) - coverage of screening lowest in provinces of Malange and Uige (‹5%) and highest in Zaire (21%) 1998 comparison5: 154,700 screened, 6,610 cases (prevalence 4.3%)	Endemic provinces: - Bengo (MSF-Belgium, ICCT†) - Kwanza Norte (ICCT, Belgian Coop., MSF-France) - Kwanza Sul (ICCT) - Malange (ICCT) - Uige (ICCT, Caritas/Angotrip, Belgian Coop.) - Zaire (ICCT, Belgian Coop.) - Luanda (ICCT) † National Programme
Central African Republic (insufficient risk data available) Total: 737 cases - Haut Mboumou: 332 (prevalence 0.9% to 1.9%) - Ouham: 351 - Nola: 10 - Lobaye: 9 1998 comparison: 1,068 cases	Foci: - Haut Mboumou (MSF-Spain) - Ouham (Programme National) - Nola (Programme National) - Lobaye (Programme National)
Democratic Republic of Congo (12.6 million at risk) Total: 2,252,671 screened; 10,369 cases (prevalence 0.4%) - Bandundu Nord/Sud and Kasaï: ›2,000 - Equateur Nord: ›1000 - prevalence › 1% in Kasaï, 0.4-0.6% in Bandundu Nord/Sud, Kinshasa, Maniema/Katanga, Orientale - ›95% of screenings active except for Equateur Sud (67%) - 51% of cases detected actively 2001 comparison: 1,940,397 screened, 17,322 cases (prevalence 0.9%, range 0.2% to 1.8%)	Provinces: - Bas Congo (FOMETRO, PNLTHA†) - Bandundu Nord (FOMETRO, PNLTHA) - Bandundu Sud (FOMETRO, PNLTHA) - Equateur Nord ((MEMISA, CDI, MSF-France, PNLTHA) - Equateur Sud (MSF-Belgium, PNLTHA) - Kasaï (FOMETRO, PNLTHA) - Kinshasa (PNLTHA) - Maniema/Katanga (PNLTHA) - Orientale (PNLTHA) PNLTHA and NGO work is largely funded by the Belgian Cooperation. † National Programme
Republic of Congo (insufficient risk data available) Total: 859 cases - MSF-Holland programmes: 152,747 screened, 733 cases (prevalence 0.5%) - MSF-Holland programmes have now closed, but one mobile team remains to do routine screening in Gamboma, Nkayi and Mossaka. 2002 comparison: 1,005 cases	Foci: - Nkayi, Bouenza region - Ngabe, Pool region - Gamboma, Plateaux region - Mossaka (Cuvette Est region) - Mindouli (Pool - to be explored by MSF-Holland) (Programme National has minimal structures and low screening capacity)
Southern Sudan (no overall risk data found) 1999 comparison[15]: 67,181 screened, 4,323 cases (prevalence 6.4%) - only three counties were covered by treatment programmes (Tambura, Maridi, Yambio)	Endemic counties: - Tambura, Ezo (MSF-Spain) - Yambio (no treatment centre; MSF-France found prevalence ‹1% in 2003-2004) - Ibba (MSF-France, closed in March 2005) - Maridi (no treatment centre, surveillance by MSF-France) - Mundri (MSF-France, stage 1 treatment by Samaritan's Purse) - Yei (Malteser) - Kajo-Keji (MSF-Switzerland) - Magwi (Merlin; no active screening)

Source: MSF HAT working group; WHO/NTD; WHO-AFRO; others as cited

The proportion of stage 2 cases has remained roughly constant over time within each site. Stage 2 patients have usually comprised approximately 60% of all the cases treated. However, they were a minority in the RoC sites (MSF-Holland), where screening has been most extensive (compared to disease prevalence).

Available data for the high-burden countries in 2004 indicate a globally declining trend over the past five years, with a national prevalence of 0.6% in Angola (down from 4.3% in 1998), 0.4% in DRC (0.9% in 2001), and 0.5% in RoC (see Table 4).

Elsewhere: low-level endemicity persists

The situation in what may be hundreds on non-epidemic foci outside of the above countries is very difficult to assess. Low-level endemicity continues in historical foci of Chad, the Ivory Coast, Gabon, Benin and Cameroon.[18] In these foci, a typical pattern is observed: as control activities are relaxed, a resurgence of cases, consisting of small but worrying localised outbreaks (caseloads in the hundreds), are observed. Screening campaigns are then organised and the cycle continues.[18,19] A relatively recent development is the spread of HAT to urban areas such as Kinshasa, DRC.[20]

The problem of surveillance

In 2001, it was estimated that **only 6% of the population living in tsetse-fly-infested areas and at risk for HAT (nearly 60 million) were under surveillance**.[18] The situation may have improved somewhat since then thanks to improved access to certain areas (such as in post-conflict Angola). At the very least, geographic proximity to NGO HAT programmes probably ensures some degree of passive surveillance in areas of unknown HAT status.

At least one treatment agency seems to be operational in each affected province/region, with the possible exception of some regions of southern Sudan. However, no comprehensive list of either current HAT foci or of agencies operational in HAT, appears to be available. **Screening coverage remains low compared to the stated at-risk population** (8.9% in Angola, 17.6% in DRC). Areas with a high suspected caseload, or historically known to be very affected, tend to be prioritised for screening, so it is reasonable to imagine that at-risk populations not screened may have a lower incidence of HAT. It is also likely that the assessment of at-risk populations is an overestimation, since it is merely based on proximity to tsetse breeding sites. However, in the absence of a test with high specificity, HAT goes undetected by health systems. Screening is therefore the only available tool to perform HAT surveillance, and it has been repeatedly demonstrated that passive detection of cases from outside the area under screening captures a minimal proportion of cases, and that this proportion decreases with distance[2]. For these reasons, **there is little justification for assuming that no HAT transmission is occurring in areas where screening is not carried out**. Although it is likely that major epidemics would have been recognised by now in these areas, these remain grey areas on the map of HAT burden.

Furthermore, at the time of writing, many countries (such as Ghana, Nigeria, Liberia, and Sierra Leone) remain without a HAT programme and surveillance system, so that **new foci of infection could well be developing but passing unnoticed**.

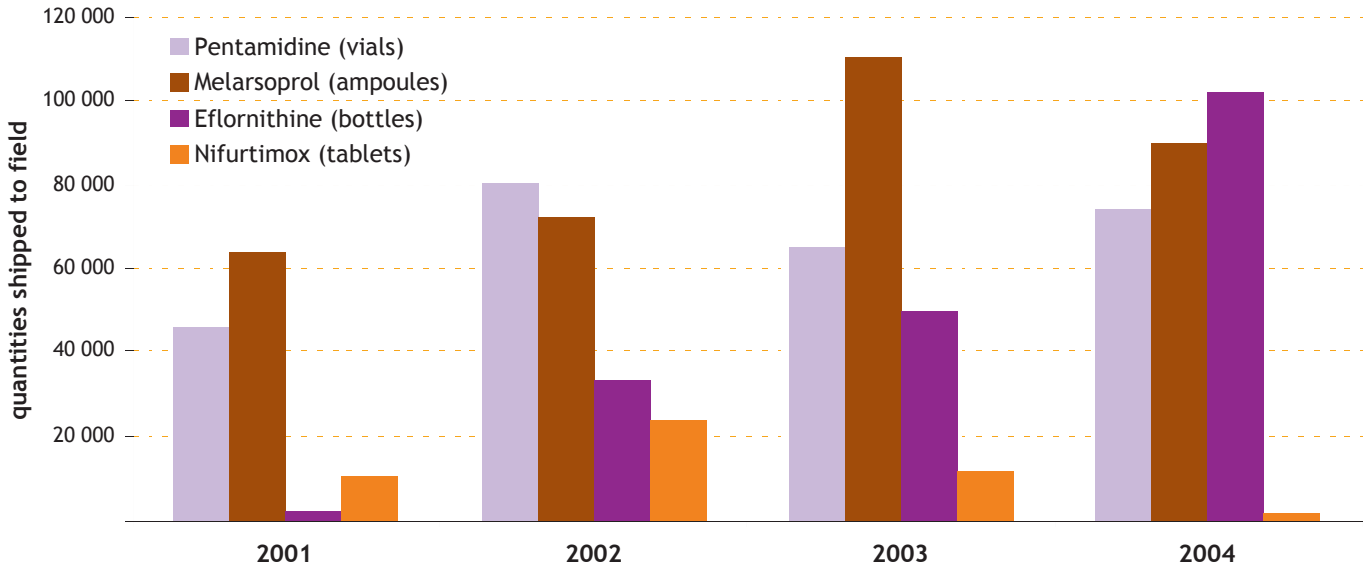
2.2 Four years of drug donations

Evolution of donations and drug consumption

Drug supply data from MSF-Logistique's WHO-Aventis-Bayer donation stock show **a steadily increasing demand for HAT drugs since the start of the agreement** (Figure 4). In particular, demand for eflornithine has risen 50-fold from a mere 1,908 bottles in 2001 to 101,760 bottles in 2004. This is counterbalanced by a decline in melarsoprol shipments from 2003 (100,450 ampoules) to 2004 (90,100 ampoules). This decline could partially be explained by a decreased need for second-line treatments as a result of the deployment of eflornithine as an effective, first-line treatment in foci characterised by melarsoprol resistance and where sufficient capacity exists to administer eflornithine. It may also reflect reluctance to use melarsoprol and difficulties in obtaining it. These data should be interpreted with caution, since orders reflect best estimates of future need: the drugs (which have a shelf-life of three to five years) may actually be kept in storage until a later year, meaning that orders received in any year may actually be used up to a year or two later.

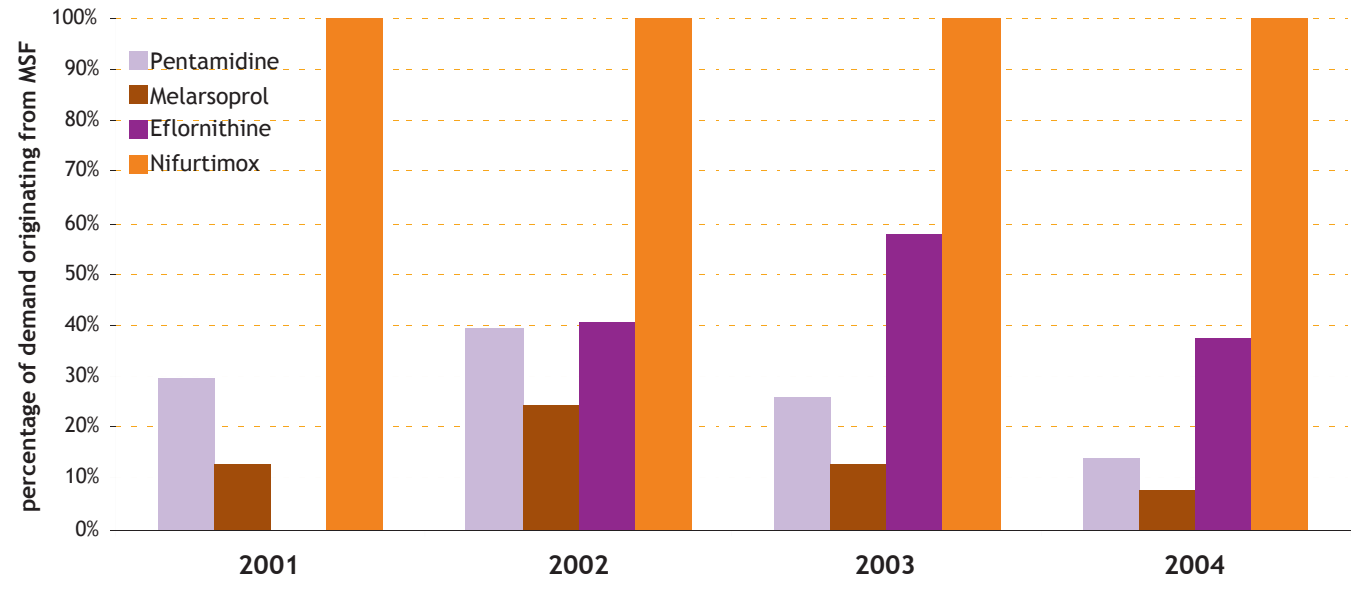
In the last three years, there appears to be a decline in the demand originating from MSF (Figure 5). This probably reflects the increased treatment capacity of other agencies, especially in Angola (10,000 melarsoprol ampoules ordered by other organisations in 2002 vs. 16,500 in 2004) and DRC (35,400 in 2002 vs. 50,300 in 2004). Nifurtimox is an exception, as all of the demand has originated from MSF (data presented exclude orders to treat patients with Chagas

Figure 4. Quantities of HAT drugs from donation stock shipped to field treatment programmes, by year and drug (year 2001 includes only second semester)



Source: MSF-Logistique

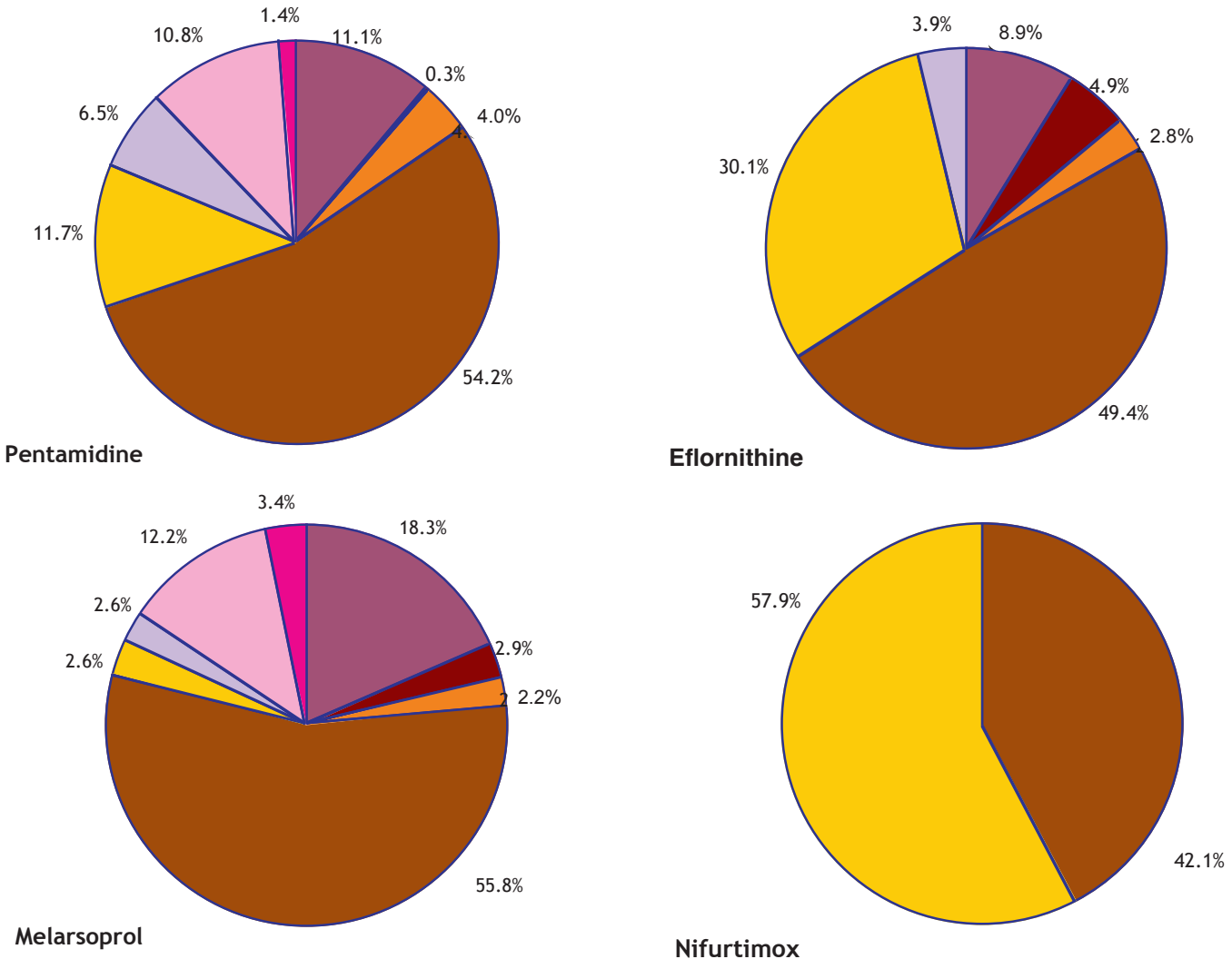
Figure 5. Proportion of demand originating from MSF sections, as a percentage of all shipments from the donation stock (year 2001 includes only second semester)



Source: MSF-Logistique

disease in the Americas). In 2004, as in previous years (data not shown) **about half of the demand originated from DRC** (Figure 6). Pentamidine shipments are probably the best indicator of demand, since all countries use it (in the same regimen) for stage 1 treatment.

Figure 6. Proportion of demand per drug by destination country in 2004



Source: MSF-Logistique

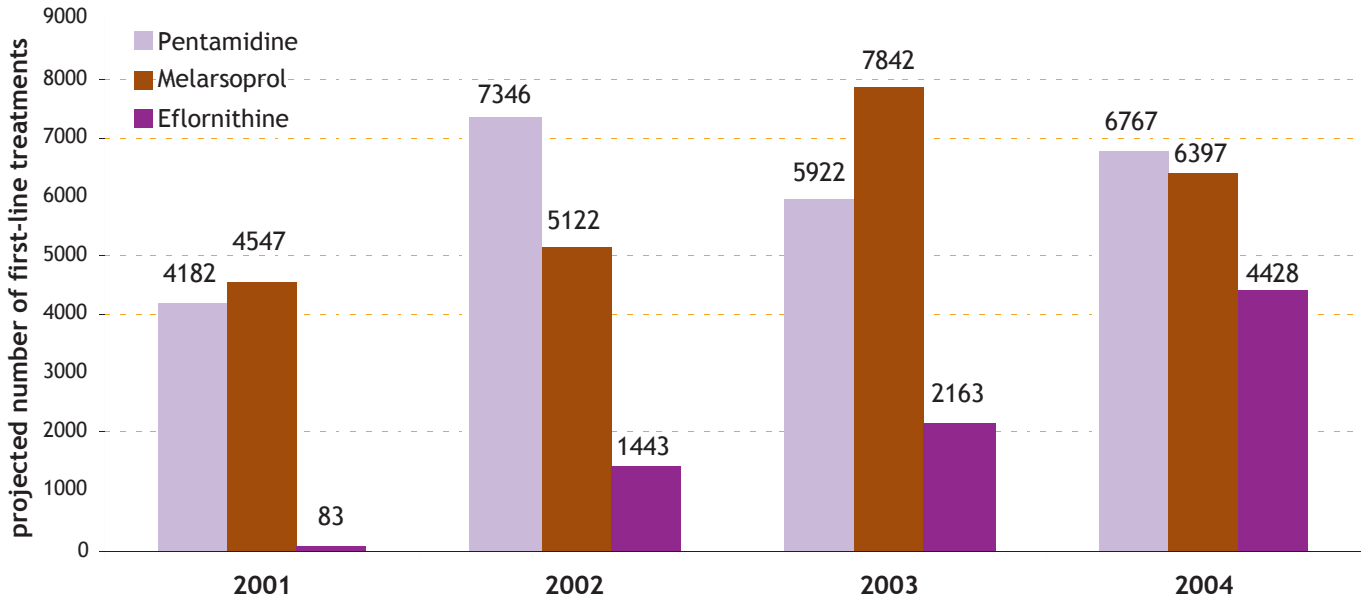
A very rough estimate of what these orders signify in terms of the number of first-line treatments is provided below, based on standard treatment regimens described by the WHO[19]. Estimates were based on the following assumptions:

- Children under 15 years of age make up 23% of all those treated[6] and have a mean bodyweight of 20 Kg; adult patients make up 77%, with a mean bodyweight of 55 Kg (weighted mean bodyweight for all age groups: 47 Kg);
- All drugs are used for first-line treatments (in reality up to 35% of patients may require second-line therapy where melarsoprol is used and resistance occurs);
- All melarsoprol is prescribed in the three-series for three days regimen;
- Drug wastage is 40% (this estimate is based on a comparison of cases actually treated and quantities ordered in MSF programmes†).

As shown in Figure 7, stage 2 treatments are increasingly eflornithine-based. Every year, roughly 6,800 *gambiense* stage 1 treatments (pentamidine only) may be administered. Assuming that stage 1 diagnoses are only 40% of the total (as observed in MSF programmes), **a total of 17,000 *gambiense* HAT treatments per year can be projected for Africa as a whole**. This estimate has a wide margin of error and should only be considered indicative. It is, however, strikingly similar to the total of 17,036 cases brought to the attention of the WHO in 2004, and may thus be a reasonable proxy of actual treatment output.

† Information received from MSF-France

Figure 7. Projected estimate of first-line treatments (based on orders from 2001-2004)



MSF field experience with eflornithine

MSF has taken the lead in adopting eflornithine as first-line therapy, replacing melarsoprol and has introduced it in its field programmes in Angola, CAR, RoC, southern Sudan, and Uganda (now handed over to the Ministry of Health). Evaluating effectiveness means checking patients at the mandatory 6, 12, 18 and 24-month follow-up visits for disease relapse. **As of December 2005, more than 4,000 stage 2 patients had received a first-line, 14-day regimen of eflornithine in MSF projects**.

Available data confirm the low toxicity of the drug: only 31/2,889 (1%) of patients died while on treatment (mostly from HAT-related complications), compared to the usual 5% or more when using melarsoprol. In Kajo Keji, southern Sudan, a cohort of 251 patients treated with eflornithine as part of the treatment programme experienced significantly lower case-fatality (0.8% vs. 3.5%) and incidence of serious adverse events, including encephalopathy (0.4% vs. 11.3%) than a previous cohort (n=708) treated with a ten-day course of melarsoprol[20]. Just published data gathered in RoC provide further evidence of a lower risk of death for patients during eflornithine treatment (1.7% v 4.8%) and relapse at one year after discharge (8.1% v 14.0%) compared to those using melarsoprol[21]. Other adverse events, such as fever, hypertension, rash, and tremor were significantly less frequent in the eflornithine-treated group, although mild diarrhoea occurred more often with eflornithine.

Data on the relapse rate after 24 months in southern Sudan and Angola are currently under analysis or being prepared for publication. Preliminary results, however, are promising: out of 249 patients followed for 12 months in Kajo Keji, only 3.6% experienced a relapse, whereas in nearby Ibba/Kotobi, the 24-month relapse rate among 2,094 patients was 6.8%20, comparing favourably with melarsoprol. **Strong evidence demonstrating the superiority of eflornithine compared to melarsoprol as first-line treatment for stage 2 HAT is accumulating, both in terms of safety and efficacy** (at least in areas where resistance to melarsoprol occurs). Today, eflornithine is the gold standard for stage 2 treatment. The administration of eflornithine requires inpatient capacity, 24-hour nursing care and medical supervision. It should be noted however that the overall benefit to the patients outweighs these difficulties. At the same time, even though the actual drugs may be free, infusion materials (infusion sets, saline, syringes, catheters, and needles) increase the treatment's cost.

2.3 Diagnostic problems

Ideal qualities of a HAT test

Effective HAT control requires simple but accurate detection of trypanosomal infection and classification of the patient into the right HAT clinical stage. Key ideal prerequisites for a HAT test include:

- high sensitivity (>99%), since HAT is fatal unless treated[†††];
- high specificity (>99%), since HAT treatments are costly and toxic;
- the ability to classify patients as stage 1 or stage 2 accurately, since the choice of treatment is stage-specific, and where melarsoprol is used, a misclassification as stage 2 can result in fatal adverse reactions;
- equal accuracy irrespective of trypanosome strain;
- the ability to yield reproducible results provided a minimal level of technician training;
- use to monitor the outcome of treatment over time;
- feasible to use in remote settings where mass screening is carried out;
- no requirement of a cold chain;
- ability to yield an immediate result;
- high level of safety and acceptability to the patient;
- low cost;
- easy to produce.

In reality no single HAT test is likely to include all of these characteristics. Up to now, a combination of tests has been necessary.

Constraints with current diagnostic tools

Current HAT diagnosis is far from ideal. Present options are technologically outdated and remarkably complex given the contexts in which treatment agencies tend to operate. Over the years, complicated diagnostic algorithms have been set up that combine a variety of tests performed on the same patient (Figure 8). These algorithms are necessary because no single test is sufficiently sensitive and specific, and because some tests can only be performed at the referral centre level and are time-consuming and dangerous. The epidemiological and technical considerations underlying HAT tests and algorithms are manifold and complex, and beyond the scope of this document, but a good review of HAT diagnostic options was recently published[22].

There are essentially three steps involved in diagnosing HAT:

1) Screening: This relies largely on the Card Agglutination Test for Trypanosomiasis (CATT), developed in the 1970s. This rapid, simple test, performed on undiluted capillary blood, has an acceptable (but not perfect) sensitivity (87-98%) and low specificity. The CATT's utility is primarily at the mass screening level. However, the test is also used at different dilutions of blood to aid in final diagnosis (as the dilution decreases, sensitivity decreases but specificity improves). Patients with a positive CATT result but no confirmation of infection (see below) are usually considered as serological suspects and re-tested at three-month intervals in some MSF programmes. CATT currently costs US$ 0.42 /test, or up to US$ 0.84/diagnosis (since usually two CATT dilutions are attempted). The apparatus to perform the test costs US$ 398[†].

2) Parasitological confirmation: This step currently requires microscopic observation of trypanosomes. Several techniques are available for this, and each has serious drawbacks; moreover, sensitivity is a problem with all of them since parasite density in HAT is often as low as 100 parasites/mL (i.e. below the detection threshold). The main techniques used in the field are[22]:

- microscopic observation of fluid aspirated from the lymphatic glands of patients who display trypanosomes after palpation (this sign, however, is not ubiquitous, and sensitivity of this technique varies from 40% to 80%);
- microscopic observation of blood after a preliminary step of centrifuging capillary blood so as to concentrate the parasites and improve the chance of detecting them under the microscope. Three techniques based on centrifugation are currently in use:

††† Sensitivity is the extent to which the test is able to detect positive cases (thus, a very sensitive test misses very few cases). Specificity is the ability to detect the truly positive cases (thus, a poorly specified test yields many false positive results). In order to maximise both sensitivity and specificity, a series of different tests may be applied sequentially or simultaneously on the same patient according to a pre-defined diagnostic algorithm.
† Information received from the Prince Leopold Institute of Tropical Medicine (ITG)

• microhematocrit centrifugation technique, or Woo test (developed in the 1970s), which consists of a technique simple enough that it can be applied during mass screening;

• Quantitative Buffy Coat (QBC), a variant of the Woo test that relies on fluorescent staining; the technique can only be performed in referral centres but has a high sensitivity level;

• mini-anion exchange column technique (mAECT); developed by Belgium's Prince Leopold Institute for Tropical Medicine (ITG) and currently produced in Kinshasa, DRC. This chromatographic tool achieves a sensitivity level that is higher than the Woo test and comparable to the QBC test.23 However, it is more laborious and expensive than other blood detection techniques.

3) Stage classification of parasitologically confirmed cases: This final step relies on the detection of either trypanosomes or an elevated white blood cell (WBC) count in the cerebro-spinal fluid (CSF), an indirect indication that infection has crossed the blood-brain barrier (i.e. progressed to stage 2). CSF is collected through lumbar puncture, a procedure that is both dangerous and painful for patients. Trypanosomes are difficult to detect in the CSF, so in practice the WBC count often determines the staging decision. Different agencies use different WBC thresholds to guide treatment: most give pentamidine to patients with 5 or fewer WBC/µL and stage 2 drugs for higher WBC counts. There is however some evidence that pentamidine is effective in some patients with up to 20 WBC/µL in the CSF. Patients with WBC counts of 6-19 WBC/µL are sometimes considered "intermediate stage", and, in Angola, receive pentamidine.

The major constraints of current HAT diagnostic tools include:

• **inadequate human resources:** health staff is lacking and laboratory technicians must be highly skilled in using the various techniques;

• **reliance on electricity;**

• parasitological confirmation and **staging is difficult to perform** at the mass screening/community level;

• **complicated programme logistics:** a variety of tests, testing kits, reagents and spare parts must be kept in stock;

• **quality control is difficult to implement** due to the number of tests employed;

• **limitations of the CATT test:** the CATT test has very poor sensitivity in certain HAT foci (such as in Nigeria or Cameroon) where circulating trypanosome strains do not elicit the antibody response which CATT antibodies recognise and bind to, creating the visible agglutination reaction;

• **a lack of follow-up tests:** a non-invasive test for monitoring patients' response to treatment over the 24-month follow-up period is not available (the CATT test stays positive for many months or years following clearance of the infection); lumbar punctures are therefore necessary at follow-up visits;

• **problems involving the lumbar puncture:** The lumbar puncture is difficult to perform and very painful for patients. In addition, patients often do not return for follow-up lumbar punctures because of the painful procedure, especially when they are already feeling well;

• **under-detection issues:** the threshold of detection of parasite density is too high, thus leading to under-detection of individuals with low parasite density;

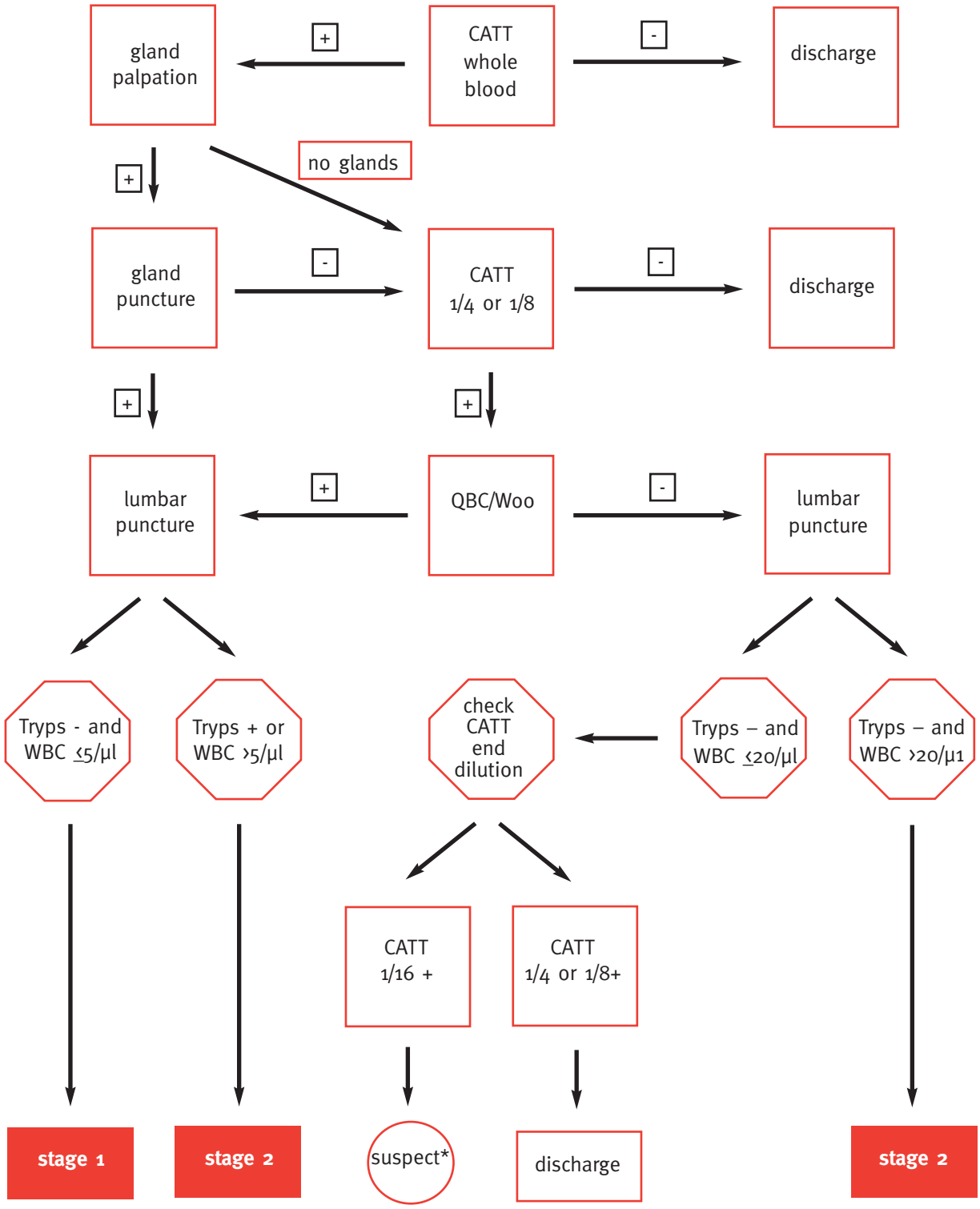
• **imprecision on white blood counts:** WBC counts, the crucial parameter for staging, are notoriously imprecise, and in children may naturally be elevated (no adjustment is made for this in the algorithms).

As with HAT drugs, production of these known diagnostic tests is not fully ensured. The CATT test is manufactured only by Belgium's ITG in Antwerp, and sold at cost. Production of the antigen requires raising and sacrificing large quantities of laboratory mice, and the technique is only mastered by a few people. Capacity for production is limited, and a previous attempt to create an additional manufacturing unit has not been successful. Nevertheless, ITG staff are confident that capacity can keep up with needs (production has been increased over the years from approximately 300,000 tests in 1987 to almost three million in 2004.*)

Despite the fact that it is more sensitive to low parasite densities than the Woo test and that it is appreciated by laboratory staff[22] due to its ease of use, the QBC test kit is no longer manufactured by Becton-Dickinson, and is therefore being progressively eliminated from diagnostic algorithms.

* Information received from ITG.

Figure 8. Example of a HAT diagnostic algorithm in use by MSF



* Treat as stage 1 only if prevalence is ≥ 2%

Source: *Sleeping Sickness: a practical manual for the treatment and control of human African trypanosomiasis*, MSF, 2005

3. Challenges for the future

3.1 Predicting future needs

The decline may continue, but reversal possible

Even though HAT may be on the decline now, this trend could easily reverse in the future as institutional and NGO interest in the disease declines. Historical evidence from all highly affected countries shows that **the price for neglecting HAT control is high, and paid in the form of dramatic, lethal epidemics which are often detected too late**. Based on published reports, the lag times between interruption of control activities following an achievement of near-zero incidence, and the recognition of a new epidemic have been approximately 11 years in Angola[5], 8-11 years in CAR, and 7 in Cameroon[18].

One of the paradoxes of HAT is that limited but thorough **control today is necessary, not only to prevent future loss of life but also to avoid having to implement massive and expensive control programmes later**. Unfortunately, it is likely that in foci where HAT morbidity and mortality are small compared to that of HIV/AIDS, malaria, tuberculosis, diarrhoeal and neonatal diseases, it will become increasingly difficult to argue that HAT control is a public health priority. Without clear political understanding and awareness of the consequences of interrupting control, **funding for HAT programmes may therefore soon run dry, and there is a clear danger that the epidemic wave of the 1990s will be repeated again**.

NGOs including MSF must rethink their operational strategies regarding HAT treatment and control. There is a need to move away from expensive, stand-alone, vertical programmes towards an integrated health care approach whereby diagnosis and treatment take place within the day-to-day activities of a basic health care programme. This will require diagnostic and therapeutic advances.

Possible new or re-activated foci

New HAT foci are occasionally discovered in areas thought to be free of the disease. Examples from the 1990s described in the literature come from central Nigeria24 and central Uganda[25], where a *T. b. rhodesiense* focus appeared in dangerous proximity to the historical West Nile gambiense focus, raising the prospect of two diagnostically indistinguishable forms occurring in the same area. In DRC, new pockets of high HAT incidence are being reported by the national programme and MSF. The circumstances around these events are poorly understood, and, at least in this above case, were not related to armed conflict or displacement. Changes in land use patterns can favour tsetse fly reproduction or bring humans and flies in closer contact (a good example of this is the conversion of natural environments into plantations, as was done in Ivory Coast)[26]. Migration and travel for economic or other reasons could also contribute to creating new foci.

Interestingly, war and conflict have had no impact on HAT epidemiology in West Africa, whereas armed conflict, directly or indirectly, led to vast HAT epidemics in Central Africa in the 1990s. In the 1940s, Sierra Leone, Liberia and Guinea experienced very large HAT epidemics, with caseloads above 100,000[3]. No new outbreak has been recorded in these countries despite years of conflict. However, surveillance for HAT is poor to non-existent in these foci due to the lack of tests and insufficient access to health care. Small HAT outbreaks can take time to develop into full-blown epidemics and the initial rise in cases usually goes undetected. Although data are missing, it is conceivable that HAT could become a serious problem in these countries again in the years to come.

Is elimination achievable?

In the 1960s, elimination of HAT from the African continent seemed tantalisingly close, but the effort was cut short before its actual feasibility could be assessed due to African nations' becoming independent and adopting new priorities. Central to this is the controversial and still unresolved question of whether human beings are truly the only carriers and transmitters of *T. b. gambiense* infection. It has been shown that a variety of animal species can be infected with *T. b. gambiense*, and that some species, notably antelopes and pigs are particularly susceptible[27]. There is however, no conclusive proof as yet that such animals can successfully transmit the infection to tsetse flies and that these in turn can infect humans, i.e. whether an animal-fly-human cycle exists. If the latter were the case, **case finding and treatment alone might never be sufficient to bring about elimination**, since new trypanosome infections would continually be re-introduced into the human population from animal reservoirs[28].

In the light of past experience, two empirical observations can be made.

- **Control efforts based on mass screening are very clearly associated with dramatic reductions in HAT prevalence**. This suggests that by far the most important transmission cycle must be human-fly-human, and that animal carriers play a minimal role, if any.

- However, despite extensive programmes involving both case treatment and fly control, **nearly all known HAT foci seem to persist over time**, sometimes maintaining extremely low prevalence (less than 0.1%). Situations such as these have been observed in Ivory Coast[29] and Cameroon[30]. Although little mathematical modelling of the risk of infection in such conditions has been carried out, it is difficult to explain how the infection could persist under such conditions given the complexity and fragility of the human-fly-human transmission cycle. The existence of a low-level animal reservoir is one possible answer.

What is evident is that even well organised programmes have so far failed to completely eliminate HAT transmission, with the possible exception of a focus on Luba island, Equatorial Guinea[31]. A WHO programme to eliminate trypanosomiasis exists nominally, but has not set any quantitative objectives[32].

The likely scenario is therefore that continued control, including mass screening, will be necessary for the foreseeable future in all highly active foci. This includes sites in which MSF was active but has now handed over to national programmes after achieving substantial reductions in HAT prevalence (e.g. to under 0.5%). It should be noted that the responsibility for keeping foci under control, possibly perpetually (or until new epidemics occur), will fall on national HAT programmes. Integration of HAT services into primary and secondary health care is likely to be attempted, but currently available tools are inadequate to fulfil this ambition. **Control strategies, as well as therapeutic and diagnostic tools, need to be adapted to provide care for HAT patients and continue active case detection within a new epidemiological context - low but persisting endemicity, and an ever-present threat of epidemic resurgence.**

What kind of drugs are most needed?

Key characteristics of an ideal drug for HAT would include:

- high efficacy
- low toxicity
- **a short regimen** (to facilitate adherence and minimise toxicity);
- an **oral formulation** with a small number of tablets per treatment course (provided that this oral regimen is also short). Alternatively a short-course injectable would be acceptable, with intramuscular injections far preferred over intravenous;
- the ability to efficiently cross the blood-brain barrier, as well as to be active against the earlier blood-lymphatic stage (so as to **cure both stage 1 and stage 2 cases**);
- **multiple mechanisms of action** against the trypanosome to minimise the risk that spontaneous DNA mutations in the parasite will easily lead to drug resistance;
- a product that is affordable, appropriate and accessible, and;
- stability under hot and humid climate conditions.

In the foreseeable future, it is likely that **a majority of cases detected will continue to require treatment with stage 2 regimens**, especially since active screening will become infrequent once foci are brought under control, thus reducing the chances of detecting cases early.

In the field, increasing melarsoprol treatment failures are a reality. Most national programmes still rely on melarsoprol as first-line treatment. As evidence accumulates on the low toxicity and high efficacy of eflornithine monotherapy and the possible combination of eflornithine+nifurtimox, it can be hoped that treatment centres that are sufficiently well equipped to administer a complex, intravenous course of eflornithine will increasingly switch to these alternatives. **In the next five years, melarsoprol will increasingly be replaced as the first-line regimen, and, in programmes that continue to use it, rising relapse rates will cause an increase in demand for eflornithine and nifurtimox as second-line drugs. Assuming currently ongoing trials are successful; the eflornithine+nifurtimox combination may become the gold standard in stage 2 treatment by 2007/2008**.

It should be noted that eflornithine is about ten times more expensive than melarsoprol. The present WHO-Aventis-Bayer donations therefore mask a very significant increase in treatment costs, and a potential major hurdle to the deployment of these drugs. On the other hand, the eflornithine+nifurtimox combination

requires one-fourth the number of infusions compared to the standard eflornithine regimen, with an obvious cost benefit.

3.2 New tools for improved diagnosis and treatment

Research on improved diagnostics and drug regimens for HAT is more substantial today than in the past but remains frustratingly slow in its progress, due mostly to insufficient funds, a scarcity of adequate clinical study sites, and long patient recruitment and follow-up periods.

Progress in the development of diagnostic tests

Research into new or improved diagnostic tools for HAT has been greatly limited by a scarcity of funds. In February 2006, a proposal for a broad consortium effort to develop new diagnostic tests for poverty-related diseases called the Foundation for Innovative New Diagnostics (FIND) was set up with funds from the Bill and Melinda Gates Foundation. Perhaps the most important project within this proposal's portfolio is the development of a non-invasive, serological **test for simultaneous screening and confirmation**, which would rely on a synthetic and invariable (i.e. specific for all trypanosome strains) antigen. Other objectives are a test for routine staging, and a gold standard test for validation of new diagnostics and clinical trials.

Meanwhile, ongoing field evaluation of new HAT tests is extremely limited and essentially concerns a promising new method for staging, namely **LATEX/IgM**. Also developed by ITG, this test detects total IgM antibodies in the CSF (a sign of infection) and would, if validated, replace or complete WBC counting. A multi-centric ITG study of the LATEX/IgM is currently ongoing in Angola (partly funded by WHO), where, unlike other HAT-endemic countries, patients with an intermediate WBC count (6-19 WBC/µL) and no neurological signs receive pentamidine. Through a standard, two-year follow-up, this study aims to determine whether LATEX/IgM negativity would be an accurate decisional tool for prescribing pentamidine. The same study is carrying out a two-year follow-up to determine whether the indication for pentamidine treatment can indeed be extended to 20 WBC/µL, and simultaneously evaluating an alternative antibody-antigen test known as the **LATEX/Gambiense**. Results should be available in 2008.

Aside from these two tests, other techniques are under development in several laboratories worldwide. These include an oligochromatography method with excellent sensitivity and specificity[33], antibodies against galactocerebrosides and interleukin-10 as markers of stage 2, and the Loop-Mediated Isothermal Amplification (LAMP). These methods, however, remain highly sophisticated for now and may not have an application in routine field HAT programmes.

Evaluation of improved regimens

Most current HAT treatment studies aim to shorten treatment, improve administration (i.e. oral), and prevent resistance to existing treatments (Table 5). **These studies are vital to filling the gap** until new drugs come on line. As with other diseases (tuberculosis, HIV/AIDS, malaria), it is recognised that combining drugs may be the only way to preserve them against resistance. Partner drugs ensure mutual protection by decreasing the odds of resistance developing and suppressing strains resistant to either drug with immediate benefits for the patient (recovery) and long-term benefits for the community (no transmission of resistant strains to other patients). In the case of HAT, **the development of eflornithine resistance would be a public health disaster** as no new drug for stage 2 HAT is likely to enter the market for the next eight to ten years. It is therefore widely agreed that eflornithine should be combined with a partner drug as soon as possible. Other good reasons for combining HAT drugs are to reduce the dosage and duration of treatment (and thus cost, hospitalisation time, and toxicity) and improve overall cure rates. The two most important research efforts currently taking place to improve the performance of available drugs in stage 2 HAT treatment are summarised below.

1) Development of the eflornithine+nifurtimox combination. "Proof of concept" results that this combination deserved further testing came from two MSF/Epicentre studies in Uganda: a randomised clinical trial (54 patients)[Priotto, in press] plus a case series (31 patients), which suggested a 10-day regimen of eflornithine and nifurtimox was less toxic and more efficacious than the two other possible combinations - melarsoprol+nifurtimox and melarsoprol+eflornithine. A multicentric evaluation of a simplified combination of 7-day, twice-daily eflornithine and 10-day nifurtimox for stage 2 treatment compared to the standard eflornithine treatment (14 days, 4 infusions per day) is now ongoing (note the significant reduction in eflornithine dosage and frequency of the infusions). This controlled clinical trial of eflornithine + nifurtimox (the NECT trial) was started by MSF/Epicentre in RoC in 2003 and was later extended to several sites: three

more sites supported by DNDi in DRC starting in 2005 and another two sites in Uganda supported by TDR, starting in 2005 and 2006. Taken together, the results of these three studies should provide the evidence base on the safety and efficacy of this new treatment protocol, and form the basis for a WHO recommendation for its use.

To date, data for the first 103 patients recruited in the NECT study in Nkayi, RoC have been analysed, showing that both treatments were comparably well tolerated. With 18 months of patient follow-up completed, there were two relapses in each arm, which are very promising preliminary results. A complete safety and efficacy analysis of these 103 patients is expected by the end of 2006. The final results of the full study population of 280 patients is expected in the second half of 2008. **If initial results are confirmed, the eflornithine+nifurtimox combination is likely to be a shorter, less toxic, and more efficacious cure than melarsoprol**. This new schedule, though far from an ideal solution for HAT, remains the best hope for patients in the near future.

2) Oral eflornithine. The development of oral formulations of available HAT drugs would be a major breakthrough since it would greatly simplify administration and thus enable treatment at peripheral sites. Intravenous eflornithine in its current regimen requires 24-hour supervision for 14 days due to the 4 times daily infusion protocol and infections resulting from non-sterile infusion are common. Unfortunately, to date **oral eflornithine studies have not yielded promising results** due to its low potency combined with insufficient absorption of the oral formulation leading to a lack of efficacy[34]. Administration is also a constraint since the dose required is so high that patients would have to ingest vast amounts of tablets. Because oral eflornithine has been noted to produce considerable gastro-intestinal side effects, it is feared that tablet absorption would be further compromised. Because this study would have to be followed by a larger phase III efficacy evaluation, if successful, it is unlikely that the TDR's oral eflornithine project will be completed before 2010. One hope is that combining lower doses of oral eflornithine with (oral) nifurtimox will achieve adequate cure rates; DNDi is currently supporting preliminary laboratory studies on this topic at the Swiss Tropical Institute (STI) in Basel.

As regards stage 1 HAT, interest in a shorter course of pentamidine remains, not least because such shorter regimens were used in the past, and little scientific rationale exists to justify the use of the 7-day regimen. A TDR-supported trial of 3-day versus 7-day pentamidine implemented in DRC included 114 patients in each arm up to 2002, but did not produce conclusive data due to lack of follow-up over two years.

Increasing access to existing HAT drugs

Over the long term, the challenge of ensuring affordable, quality, and sustainable production of HAT drugs, and in particular eflornithine and nifurtimox, remains daunting. Sanofi-aventis representatives report that production of the raw material needed for eflornithine is currently being done by Scinopharm (Taiwan). On the other hand, melarsoprol manufacture is likely to remain within sanofi-aventis, since the industry perceives this drug as obsolete, and due to concerns about availability of the raw material and the complexity of its production. It should be noted that, as part of the new WHO-sanofi-aventis donation agreement, HAT drugs produced by generic manufacturers will continue to be donated by sanofi-aventis and the company will accept liability for drug quality. Furthermore, given the lower production costs in the new facilities, more funds in the donation package are likely to be available for non-treatment activities (e.g. research and general control).

In spite of mounting evidence of the fact that eflornithine is a much safer treatment option than melarsoprol, very few patients outside of MSF programmes, have access to this treatment. Expensive materials such as infusion kits, fluids, catheters and needles put the treatment beyond reach of most patients even though the drug is free.

Development of new drugs

Compared to the last 15 years, there is currently a revival of HAT drug research and development. Unfortunately, **most research into new drugs for HAT is far upstream in the development process**, and is carried out mainly at the laboratory bench-side discovery stage (Table 5). Whereas discovery and in vitro validation of candidate drugs may be a relatively short process (1-2 years), the subsequent steps leading to registration for human use (animal testing, phase I testing on human volunteers, phase II safety and dose-optimisation testing, and phase III safety and efficacy trials) are extremely lengthy, especially in HAT. Preparation of a study site for good clinical practice standards acceptable for drug registration, patient recruitment, and the requirement to follow patients for 18-24 months when evaluating efficacy, together mean

Table 5. Overview of current or recently completed trials and/or case series of improved monotherapies or combinations of available HAT drugs

	Study sites (institutions)	Rationale	Safety results	Efficacy results
Monotherapies				
Short-course melarsoprol	Impamel I (Angola) and II (multicentric) (Swiss Tropical Institute)	uninterrupted 10-day course vs. three 3-day series: easier, less expensive and effective, without higher toxicity	fatality as with standard regimen, but more skin reactions[35,36]	good (7% relapses), equivalent to longer regimen[35,36]
Oral eflornithine (phase II dose-finding)	Ivory Coast (TDR)	far easier to administer than IV: fewer human resources, care possible even in remote settings	frequent gastro-intestinal disturbances[34]	low; future trials to use higher doses[34]
Nifurtimox	desk analysis - literature review (TDR)	will facilitate use in HAT, especially in combination with eflornithine	data insufficient for registration	low (up to 37% relapse rate)37; fragmentary evidence[38]
Combination therapies				
Melarsoprol + nifurtimox	DRC (ITG Antwerp) Uganda (Epicentre) Sudan (MSF)	bypass melarsoprol resistance, reduce dose and hence toxicity, improve efficacy	DRC: as for melarsoprol Uganda: very toxic (fatality: 2/18 cases)[39]	DRC: low or no relapses in about 70 patients[34] Uganda: 2/18 relapses[39]
Melarsoprol + eflornithine	DRC (PNLTHA) Uganda (Epicentre)	as above	may be toxic (1/19 patients), treatment interruptions[39]	DRC: 7% relapses as second-line[40]
Eflornithine + nifurtimox	Uganda (Epicentre) clinical trial plus case series Multi-centric NECT trial ongoing: RoC, DRC, Uganda (MSF/Epicentre/DNDi/TDR and the respective national HAT control programmes)	as above; protect eflornithine against resistance and simplify regimen	Preliminary findings: low toxicity, few treatment interruptions[39,41]	Uganda: 0 relapses (18 patients)[39] Uganda: 0 relapses (48 patients)[39,41] NECT trial: preliminary results: good efficacy[41]

that **a single HAT drug trial could take as long as four to five years from conception to reporting, and the entire process of development could take at least ten years**. Significant time savings are, however, possible if a drug that has been developed and/or registered for a different disease is found to also have trypanocidal properties.

Presently, only one compound (DB289, or chemically pafuramidine maleate) has reached the field efficacy testing (phase III) phase, and it is only useful for treating people in stage 1. A Bill & Melinda Gates Foundation-funded consortium led by the University of North Carolina, Chapel Hill is responsible for the drug's development alongside a commercial partner (Immtech Inc.). Phase II studies of this oral drug are complete, and have led to a doubling of regimen duration from five to ten days. A Phase III trial is ongoing in six sites (in DRC, Angola, and southern Sudan) under the coordination of the STI-Basel.

As for stage 2, the best prospects lie with the candidate drug DB844, also a diamidine from the same family as DB289 which has shown encouraging results in animals. This drug is however several years away from field testing in the base-case scenario, with no

Table 6. Overview of main ongoing initiatives to develop new HAT drugs

Drug / project	Sponsors / leading institutions	Phase of research	Notes
pafuramidine maleate (DB289)	UNC Consortium (UNC-Chapel Hill, including among others STI, Immtech, U.Glasgow), supported by Bill & Melinda Gates Foundation	phase III trial ongoing: final results for registration could be available by 2007-2008	10-day, twice-daily oral regimen, for stage 1 only; fear of low compliance/ resistance/melarsoprol cross-resistance
DB844 and other diamidines	UNC Consortium	advanced animal models (potential registration no earlier than 2012	for stage 1/2; fear of resistance/ melarsoprol cross-resistance
Nitro-imidazoles	DNDi	assessment of existing drugs and drug candidates; could have candidate for preclinical development in 2007; earliest registration in 2011	could offer crucial shortcut in development by identifying drugs already registered or researched for other diseases (mostly opportunistic infections)
identification of other potential candidates	UNC, DNDi, U. Dundee, UCSF, U. Glasgow and others	ongoing; screen and discovery phase	hundreds of compounds from different sources (synthetic and natural) being assessed; some will enter into lead optimisation in 2007

guarantee of efficacy and safety in humans.

Furthermore, there is concern that **both pafuramidine maleate and DB844 could have a short lifespan**, since they might have the same, single mode of entry into the trypanosome parasite as melarsoprol. (DNA mutations in the parasite affecting this entry route are thought to confer melarsoprol resistance). Cross-resistance with melarsoprol is therefore a possibility (still being investigated), and would greatly hamper the use of these drugs. Resistance in this case threatens all three of these drugs.

Despite the fact that a number of drug discovery projects are underway, with potentially hundreds of compounds being screened for possible trypanocidal effects, **few of these projects will lead to candidate drugs for clinical testing**. Out of these, it is to be expected that fewer still (if any) will prove sufficiently safe and efficacious to be considered for field use. Difficult administration could preclude the development and marketing of even a safe and efficacious drug, and the potential barrier of high production costs may have to be circumvented. In short, **today's greatest therapeutic need in HAT - safe, efficacious and affordable drugs for stage 2 of the disease - remains a distant goal. Although it is quite possible that a new drug will be available within the next decade, there remains a case for further acceleration and expansion of drug development efforts**. Next to the well advanced DB-programme with one clinical (pafuramidine maleate) and one discovery candidate (DB844), the best prospects for new drugs probably lie with the DNDi which, in addition to providing much-needed funding for HAT, has taken on a very important role in revitalising, coordinating, and creating links between different research efforts.

4. Discussion

4.1 Encouraging progress despite continuing threats

Compared to the situation in the early 1990s, **prospects for HAT control appear somewhat brighter now**, due to a number of factors:

- greater (though still insufficient) funding and institutional commitment to control the disease;
- a larger number of actors interested in the disease, including NGOs, leading to better coverage of active foci;
- the end of armed conflict in most of the active foci, enabling treatment agencies to gain better access to patients and of patients to treatment centres;
- availability of relatively efficacious, though difficult-to-administer drugs (eflornithine) from a well-managed, accessible stock;
- increased local human resources capacity;
- the realistic prospect of replacing melarsoprol with an eflornithine+nifurtimox combination within the next three to four years in at least a portion of HAT programmes that can implement an intravenous protocol;
- relatively well-funded, high-level research into new diagnostic and therapeutic tools.

These encouraging gains are however counterbalanced by a number of looming threats which may need to be addressed in the upcoming years.

- **The perception that HAT is no longer a serious problem**. This could make funding for this neglected disease more difficult to obtain and reduce governments' and agencies' commitment to control the disease and conduct further research on it. As a result, growing neglect could lead to more HAT epidemics.
- **Highly skilled staff trained to diagnose and treat patients with HAT are often diverted** to work in other health programmes. This lack of human resources to implement HAT programmes decreases the quality and capacity of national HAT programmes.
- **Unsustainable vertical programmes:** When some NGOs hand over vertical HAT programmes to national health authorities there is often no guarantee of continued funding or technical support to make the programme sustainable in the long term.
- **Changes in climate and land use** can easily expand the habitat of tsetse fly populations. This can increase the likelihood of human-fly interaction and contribute to an increasing number of HAT sufferers.
- **Renewed armed conflict can interrupt control efforts and field research:** This can increase human susceptibility to the disease and can create new foci when populations become displaced.
- **Development of eflornithine resistance:** Researchers and health professionals remain highly concerned about possible resistance to eflornithine which would mean health care providers would no longer have access to effective, non-toxic, first- and second-line treatments. In addition, if nifurtimox is not authorised for use within the next five years, it will mean that eflornithine must be used as monotherapy, with the consequent risk of growing resistance to it.
- **No new HAT drugs developed in the next 10 years:** If no new drugs emerge from the development pipeline in the next decade, health care providers will have no effective alternative to treat patients who experience resistance to eflornithine or when other drugs are unavailable.
- **Simplified diagnostic tests do not become available within five years:** Without new diagnostic tests, HAT services cannot be integrated into routine care. Plus, a lack of more sensitive and less invasive tests will continue to cause diagnostic headaches and lower patient compliance.

4.2 Covering the research gap

As mentioned earlier, Aventis Pharma entered into a US$25 million agreement with WHO in May 2001 to support WHO's HAT activities over a five-year period. Under this agreement, Aventis guaranteed production and the donation of pentamidine, melarsoprol and eflornithine worth US$ 12.5 million. The Aventis agreement also agreed to support disease management and control activities (US$ 8.75 million) and TDR's research and development activities (US$ 3.75 million). Undeniably, thousands of lives have been saved as a result. A second five-year agreement

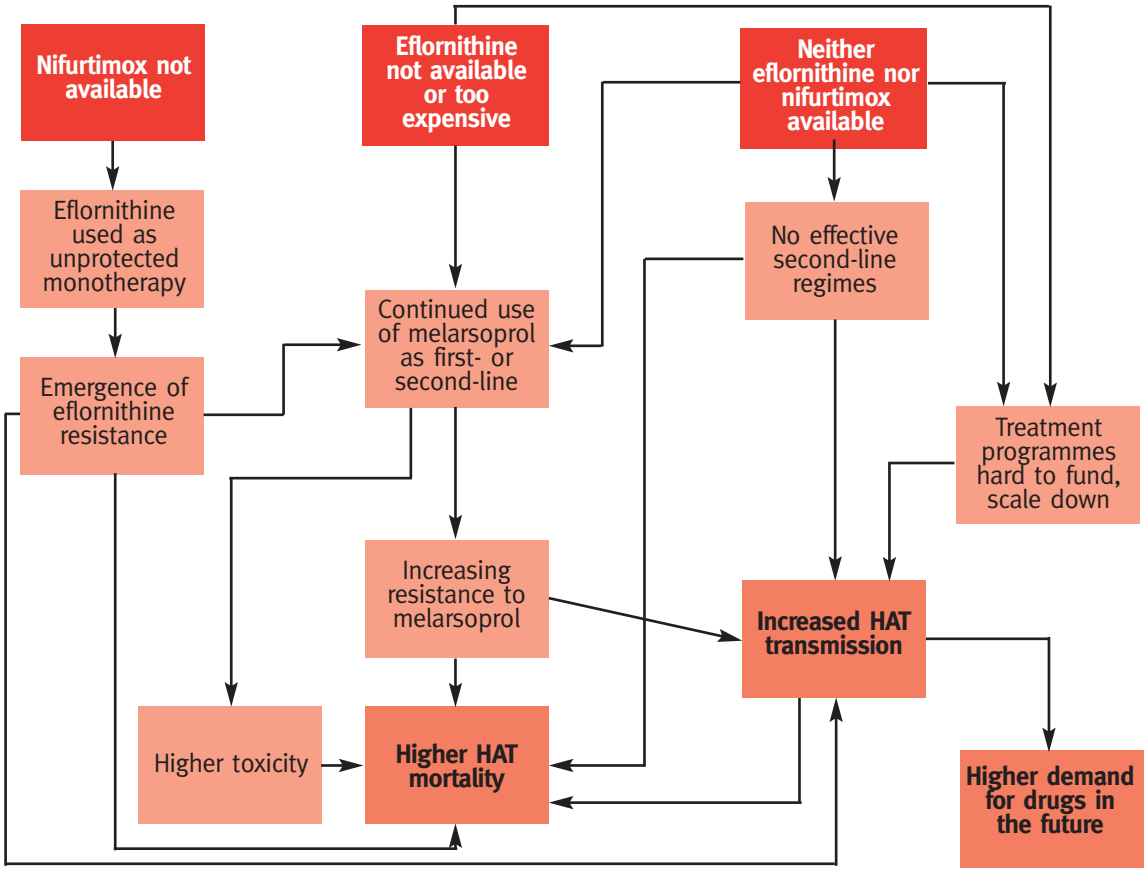
was signed between WHO and sanofi-aventis in October 2006. The new agreement consists of a donation-in-kind of pentamidine, melarsoprol and eflornithine, worth US$ 5 million and a cash donation of US$ 9.25 million with the stated objective of eliminating HAT as a public health problem in Africa. In doing so, the agreement aims to strengthen implementation activities such as case-finding, surveillance and monitoring.

The availability of nifurtimox for HAT patients continues to be uncertain. This is out of pace with the urgency of finding new cures for stage 2 HAT and demonstrates poor foresight given that the eflornithine+nifurtimox combination could well be shown to be the treatment of choice for HAT in the coming years. Not using nifurtimox in combination with eflornithine would entail a high risk of losing the most important, currently available HAT drug to resistance with no certain prospect of a replacement. WHO therefore needs to engage Bayer in vigorous discussions to ensure production and easy access to nifurtimox.

MSF continues to play a crucial role in the donations by providing logistical support for the distribution of these drugs to governmental and non-governmental treatment programmes in Africa. While it appreciates the value and necessity of these short-term donations, at the same time, it is urging WHO and others to find a way to guarantee a long-term supply of nifurtimox that does not depend on donations and to make it more easily accessible to treatment programmes. MSF is also calling for more public involvement in setting priorities for research and development on aspects of the disease and its treatment and in the allocation of funds for drugs and diagnostics.

The most likely consequences of eflornithine and/or nifurtimox non-availability are presented below (Figure 9). The resulting continued use of melarsoprol and/or eflornithine in monotherapy would, in the long run, be responsible for both increased mortality and increased HAT transmission. In general, non-availability of drugs would actually increase drug needs, thus creating a vicious cycle.

Figure 9. Schematic showing of expected effects of non-availability of eflornithine, nifurtimox, or both



4.3 Innovative tools needed to improve care

An extension of the sanofi-aventis and Bayer donation agreements does not decrease the urgency of developing the eflornithine+nifurtimox combination, gathering sufficient data on nifurtimox, finding new producers of these drugs, and continuing more aggressively than ever the research for new effective and affordable drugs.

While the development of oral DB289 for stage 1 treatment is promising, it is somewhat surprising that this project is moving faster and supported by more funding than any other, especially considering that:

- The present treatment for stage 1, pentamidine, works well, is relatively safe, and has not been compromised by parasite resistance in more than 50 years of widespread use.
- A 3-day regimen of injectable pentamidine could be equivalent to the 7-day standard, is probably easier to manage than a 10-day course of twice-daily oral DB289, and should therefore be evaluated in a clinical trial.
- There is a very broad consensus that the real need in HAT treatment today is for new regimens against stage 2.

In the best case scenario, a useful drug for stage 2 HAT could probably complete registration no sooner than 2011. As there is no guarantee that this will indeed occur, the demonstration of efficacy and safety of eflornithine+nifurtimox, and a recommendation supporting its use as first-line treatment for people with stage 2 HAT could not be more urgent.

Simplifying diagnostics is key to moving away from expensive, vertical HAT treatment programmes and to making treatment available in basic health care structures in a cost-effective and accessible way. The most pressing needs continue to be for a highly sensitive, specific and simple screening confirmatory test (possibly based on serology) and an accurate, non-invasive test to determine the disease's stage. FIND has started work on researching and developing new diagnostic tools for HAT, however, results cannot be expected earlier than 2009.

4.4 The role of MSF

In recent years, MSF has accounted for approximately one-fifth of the total number of patients being diagnosed and treated. Moreover, the organisation is also entirely responsible for efficient supply and distribution of all HAT drugs. In association with Epicentre and DNDi, it is currently implementing the most crucial study of HAT treatment in years (the NECT trial of eflornithine+nifurtimox). MSF is also a founding partner and a driving force behind the Drugs for Neglected Diseases initiative (DNDi) which stimulates and oversees some of the most promising and most needs-driven projects on HAT drug discovery and development. Finally, MSF, through its Campaign for Access to Essential Medicines, is probably among the most authoritative and vocal advocates of HAT patients' needs. It is very doubtful that without this advocacy the production of all HAT drugs would have been ensured to this day. **Above and beyond mere case finding and treatment, MSF has become essential to global efforts to control HAT**.

MSF's efforts so far have proven to be a good investment. However, much of the above gains risk being lost if MSF disengages from treatment programmes. Continuing to treat patients in the field is absolutely essential to drive research and development of diagnostics and treatment as well to raise awareness of the plight of patients affected by this disease.

There is an increasing realisation that new operational models are needed for HAT treatment and control programmes to be sustainable. With downward trends in prevalence, it is time to move away from expensive vertical programmes to cheaper and integrated health care at peripheral levels of care. For this to happen, new diagnostic tools and therapies are needed. MSF therefore needs to renew its commitment to care for and treat people with a disease that will soon fall off the agenda of international donors and national programmes.

5. Conclusions and recommendations

MSF recognises that important actions need to be taken in order to improve HAT control, screening efforts, testing and treatment. In addition, MSF sees the need for more field operational research to explore new diagnostic, therapeutic and operational options in the absence of other actors. The organisation also plans to continue documenting and disseminating data on its own field experience and to advocate for the patients who suffer from this treatable disease, while working with partners such as DNDi, FIND, TDR, WHO and drug companies to address a disease that has been neglected for ages.

It calls on all of the actors involved in combating this health problem, including national governments, international agencies and organisations, fellow NGO treatment programmes, and the research community to prioritise the follow areas:

National programmes and NGOs are urged to:

- Work on **new operational models** now that the decline in prevalence has made resource-intensive, vertical HAT programmes impossible to sustain. NGOs (and national health programmes) need to find ways to ensure better service delivery in order to maintain health service capacity in low-prevalence areas.

- **Improve quality of health care** provided in health centres so that HAT patients receive the best available drugs for stage 2 treatment, namely eflornithine and eflornithine-based combination therapy rather than the more toxic melarsoprol.

National governments, WHO and international donors are urged to:

- **Make treatment of HAT patients a priority** and play a leadership role in global efforts to set priorities and provide sufficient funds for research and development. Public leadership on setting R&D priorities is clearly needed as the market has dismally failed to address neglected health needs in poor countries. Countries in which HAT is endemic should especially play an active role in setting priorities and promoting R&D on tools to fight this disease.

- **HAT control should continue to be top on the agenda** of national ministries of health to help avoid epidemics of the disease and the related suffering and death they bring. Evidence has shown that ongoing control programmes are a key element in ensuring decreasing prevalence and a reduced need for treatment.

WHO, national programmes and pharmaceutical companies offering drug donations are urged to:

- **promote more effective therapies for patients** by moving away from melarsoprol use to therapies that include eflornithine in all national programmes as a first-line treatment for HAT patients in stage 2 of the disease. Providing free infusion kits will increase patient access to treatment.

- **safeguard access to all drugs effective against the parasite** by ensuring the production and easy availability of nifurtimox for governmental and non-governmental use in order to make combination therapy a reality.

Researchers are urged to:

- **Give high priority to combination therapy trials** and a speedy analysis of field trial results so that a WHO recommendation can be made in support of combination therapy.

- Conduct **more research and development** on new molecules that could provide new medicines for HAT patients. There should also be increased work done on diagnostics that are easy and safe to use taking into account changing operational models, particularly the need to focus on a more integrated health care approach to care for HAT patients.

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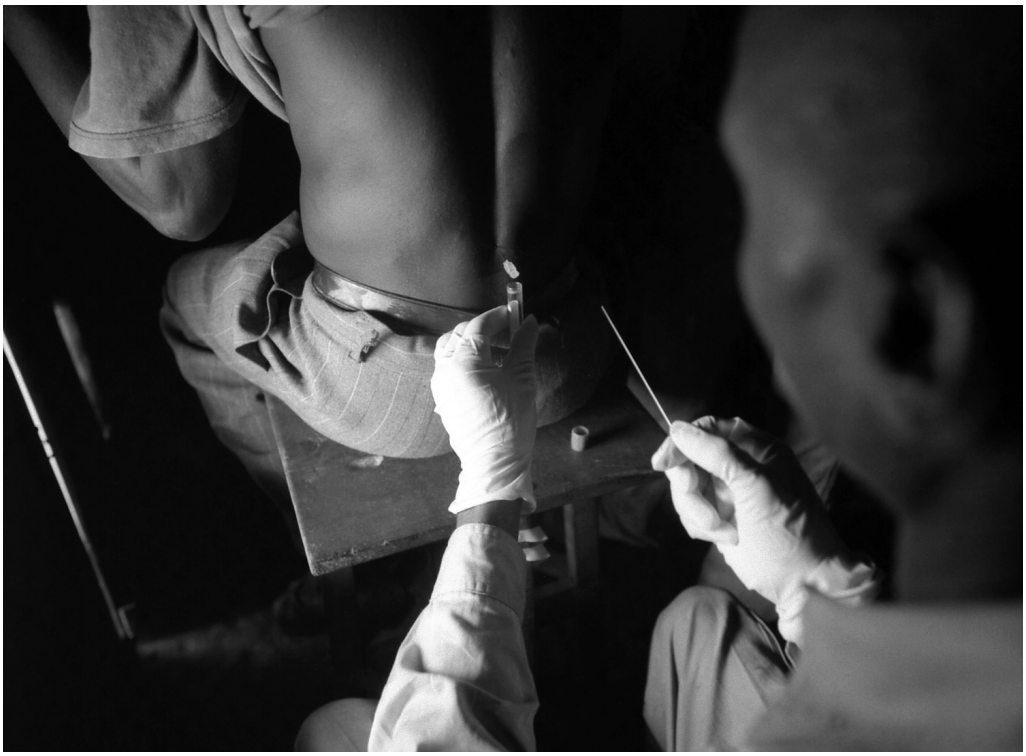
Below: A patient suspected of having stage 2 sleeping sickness must endure a painful lumbar puncture at an MSF clinic in the Democratic Republic of Congo in order to be accurately diagnosed. If found to have the disease, the patient will need to have the procedure repeated a number of times after treatment to ensure that he has fully recovered. Less invasive diagnostic tools are urgently needed to more easily and accurately diagnose and stage people with this disease.



Front Cover photo: Patients with sleeping sickness receive treatment with the drug eflornithine at an MSF project in Isangi, Democratic Republic of Congo. Although eflornithine is now recognised as a more effective treatment for patients in an advanced stage of the disease, it is often not used. Instead, an older, more toxic drug is used.

Design/artwork: Twenty3 Crows Ltd

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MEDECINS SANS FRONTIERES

Médecins Sans Frontières
Campaign for Access to Essential Medicines
Rue de Lausanne 78
CP 116
1211 Geneva 21
SWITZERLAND

Tel ++41-22-8498 405
Fax ++41-22-8498 404

access@geneva.msf.org
www.accessmed-msf.org