Human African Trypanosomiasis

Update on progress and future perspectives

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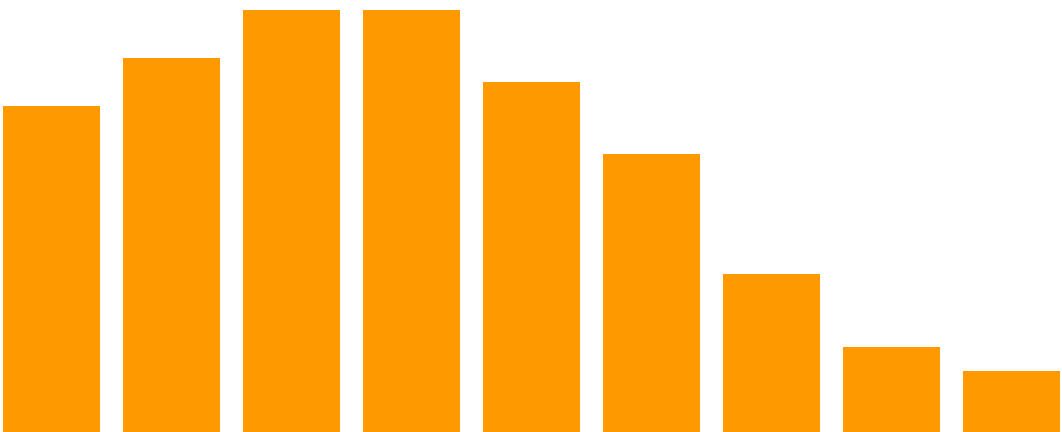

Preface

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

The information presented here is *not* intended to replace or amend either current WHO recommendations on HAT management or the MSF HAT manual. Similarly, it should not be considered as 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 stimulate MSF and others to continue in its precious work against HAT, one of the most neglected tropical diseases.

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1. Background

1.1. Main features of human African trypanosomiasis

1.1.1. The disease

Human African trypanosomiasis (HAT), or sleeping sickness, is one of the most neglected parasitic diseases, affecting about 50,000 to 70,000 persons throughout sub-Saharan Africa.[1] This WHO figure is likely to be an under-estimate as the figures are based on reported yearly 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 of cattle, and humans are only accidentally infected; this disease occurs in several foci east of the African Rift Valley. *T.b.gambiense* HAT essentially affects humans, and foci (about 200) are found west of the Rift Valley. Throughout this report, HAT is taken to imply the *T.b.gambiense* form of the disease, which currently causes the vast majority of sleeping sickness cases and deaths 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, with a duration of a few months). In stage 1, parasites reproduce in the blood and lymphatic system of the patient. In stage 2 they cross the blood-brain barrier, leading to behaviour changes, sleep alterations, immunological and organ malfunctions, severe wasting, and eventually irreversible coma and death.

1.1.2. 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 populations are affected by weather and changes in land use, fly populations alone are not predictive of 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 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 for their sustenance on scarce water sources.

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

1.1.3. Main options to control HAT

The 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:

reduce the number and life expectancy of tsetse flies so as to minimise fly-human contact and interrupt the fly-human-fly transmission cycle;

treat as many of the cases as possible, so as to reduce the reservoir of infectious individuals (prevalence).

Tsetse 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 treatment centres is simply not enough: stage 1 cases are less likely to present themselves for treatment, as distance to a health facility is almost always an obstacle in nearly all active HAT foci.[2] Active case-finding campaigns are therefore necessary, involving the travel of teams to isolated communities and the attempt to screen the entire population (Box 1). Suspect cases are then referred to specialised inpatient HAT treatment centres where diagnosis is confirmed, clinical stage determined, and treatment administered. After discharge, cases should come back 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 available drug regimens - administration is either by injection or perfusion, 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.

Box 1. Why active case finding and treatment is crucial to 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 cure, and experience less long-term sequelae than stage 2 cases
  - Cases detected early also remain infectious for a shorter period
- Dramatically and rapidly reduces infectious reservoir, and hence transmission

1.2. The last two decades: HAT's dramatic come-back, MSF's response

1.2.1. The colonial period: ravaging outbreaks, draconian control

The spread of HAT through the African continent is largely attributable to environmental and social upheavals brought about by colonial policies. Between the turn of the 19th century and the end of World War II, dramatic HAT epidemics raged in the Congo basin (500,000 deaths estimated), Uganda (200,000), 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 mass 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.

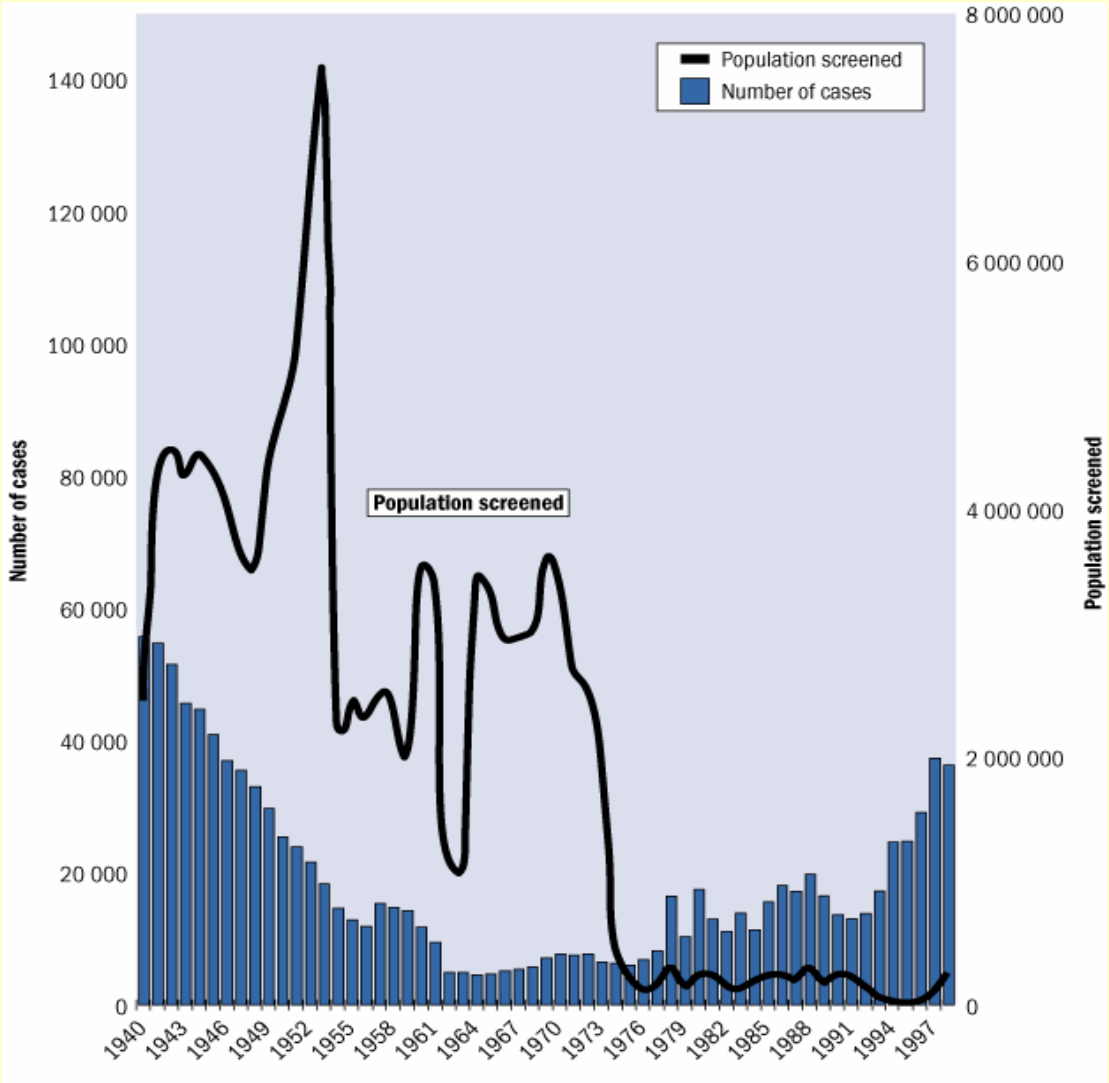
1.2.2. After decolonisation: neglect and HAT resurgence

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] With independence, many HAT-endemic African countries found themselves with scarce budgets to continue routine control activities, and lacked 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 number of persons under screening surveillance, and the corresponding resurgence of HAT in Africa from the 1970s was exacerbated by alarming epidemics in the 1990s (Figure 1). This pattern is evident in all of central Africa. For example in Angola[5] only 3 new cases were detected countrywide in 1974, compared to 6,610 in 1998. **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.**

Just as HAT became neglected in the endemic countries, so did research into its treatment and diagnosis. In particular, drug development for HAT stopped in 1949 (see below) and no new medicines appeared until the early 1990s.

Figure 1. Yearly trends in reported HAT cases and 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/emc-documents/surveillance/docs/whocdscsrisr2001.html; accessed 02/04/2005).

1.2.3. 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, these programmes screened 981,939 persons, and treated 18,132. By 2002, prevalence had been brought down significantly throughout the region, and the yearly incidence was only 6 cases per 10,000 inhabitants.[7]

Other MSF HAT programmes followed in Southern Sudan, Angola, the DRC, the RoC, and the CAR (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 become increasingly confronted with difficulties in diagnosing and treating HAT cases. In particular, it became increasingly apparent that the historical mainstay of first-line stage 2 treatment, melarsoprol, was an extremely toxic and increasingly ineffective therapeutic solution.

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 province	Belgium	2002-2003 2004-present	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, as of end 2005.

1.3. A drug crisis

1.3.1. Dire lack of therapeutic options

To date, treatment of 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 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 as first-line)	stage 2 (second-line, mostly in combination)
Mode of administration	intramuscular injection	intravenous injection	intravenous perfusion	oral
Typical regimen	daily for 7-10 days	Historical standard: three series of daily injections for 3 days, with 7 day rest periods in between series New recommendation: 10-day short regimen	four perfusions per day for 14 days (first-line) or 7 days (second-line)	three times a day for 14 days
Relapse rate	low (<5%) despite widespread past use with sub-standard doses	increasing (up to 35% according to site)	low; 10-15% at 24 months in MSF programmes	high (up to 37%) if given as mono-therapy
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 USD (year) prior to donation agreements	20-25 (pre-2000, already given at cost-recovery)	54-80 (pre-2001)	~700 (1999)	10-15 (2002)

The toxicity of melarsoprol, an arsenic derivative introduced in 1949, makes stage 2 diagnosis and treatment both very painful and highly toxic, causing death in around 5% of patients treated with it. Largely in order to minimise the risk of patients being misclassified as stage 2 and treated with melarosprol, HAT diagnosis has come to rely to on very complex algorithms (see below). The already dire situation has worsened since 1980s when increasing treatment failure rates for melarsoprol were noted by MSF teams.[8] Today, melarsoprol failure rates are as high as 31% in Uganda, 18% in Southern Sudan, and 25% in Angola.[9]

The increasing phenomenon of melarsoprol treatment failures has led to the use, on a compassionate basis, of other drug regimens that have not been formally validated, such as nifurtimox or a combination of melarsoprol or eflornithine (see below).

1.3.2. 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; it was christened the **"resurrection drug"**. Small but conclusive safety and efficacy trials followed, and the drug was registered for use against stage 2 in1990, in what was the first major breakthrough in HAT treatment research in 50 years.[11] Nevertheless, the use of eflornithine up to now has been limited by two factors:

Very high cost per treatment (around $US 700) before the WHO-Aventis donation agreement in 1999.

Very difficult administration: the drug is administered 4 times a day in 2-hourly infusions over 14 days. This requires inpatient facilities, day and night nursing care, precautions to avoid bacterial infections and relatively sophisticated and costly materials (infusion fluids, needles, catheters).

1.3.3. Drug production grinds to a halt

Throughout the 1990s, production of all three 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 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. So as 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.

Bayer also discontinued production of suramin (Germanin®), the only drug available to treat stage 1 of rhodesiense HAT.

1.4. A way forward: Bayer and sanofi-aventis drug donations

1.4.1. Bayer re-starts nifurtimox and suramin production

In good part, thanks to advocacy from 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, free supply of nifurtimox (500,000 tablets) for two years, is being donated by Bayer for use in 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 of the safety, efficacy and dosing of nifurtimox for use in HAT, as part of a recently negotiated (2004) Bayer-WHO/TDR Clinical Trials Material Supply Agreement making available for use 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 (see below).

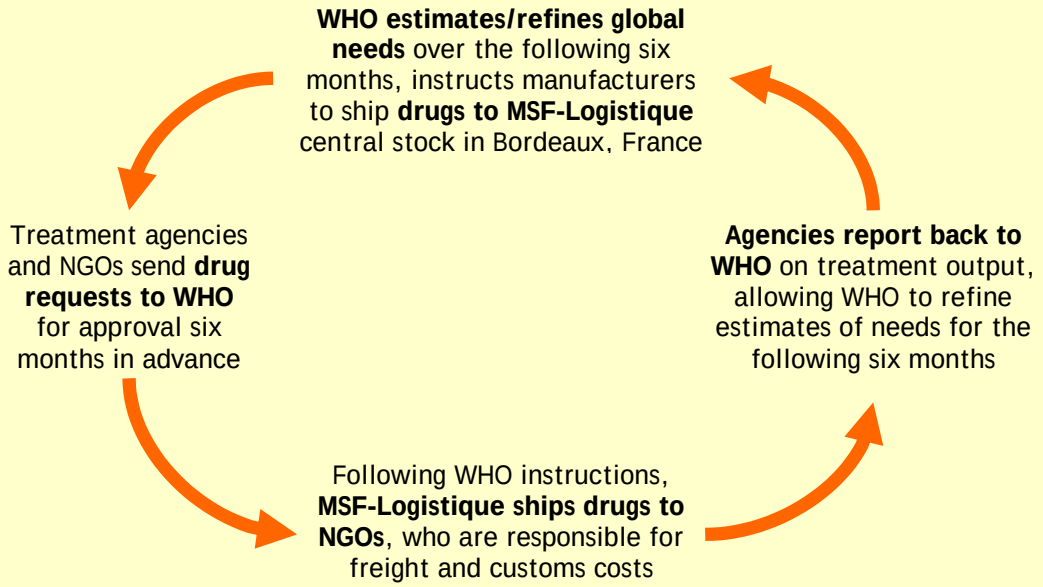
This legal starting point (which is not equivalent to a donation) also enables **limited compassionate use of nifurtimox for therapeutic purposes**. At the time of writing, this is a **"Named Patient Programme"**, requiring detailed monitoring and documentation of the medical file for each patient treated 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 Ministries of Health, who must agree to accept liability in case of drug-related adverse events. However, to date the use of nifurtimox in the field has been hampered by considerable bureaucratic obstacles.

1.4.2. WHO and Aventis sign agreement on nifurtimox, melarsoprol and eflornithine

Just as Aventis Pharma's eflornithine production faltered, another company, Bristol-Myers Squibb, launched a 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 campaign that led to an agreement between WHO and Aventis, also involving Bristol-Myers Squibb, being reached in May 2001. MSF was instrumental in the negotiation of this agreement, and continues to provide much of its logistical backbone.

Oversight of each drug donation passes through WHO's Communicable Disease Surveillance and Response department. sanofi-aventis and Bayer ship drugs to MSF's logistics centre in Bordeaux, France, from which supplies are sent out to all recipient agencies, following instructions from WHO (see Box 2).

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



As part of a previous License agreement (1999), Aventis had already agreed to hand over license rights and manufacturing know-how 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 into improved or new HAT drugs.

During this period sanofi-aventis has managed to secure availability of raw materials and production of eflornithine. Eflornithine is now produced by Scinopharm in Taiwan.

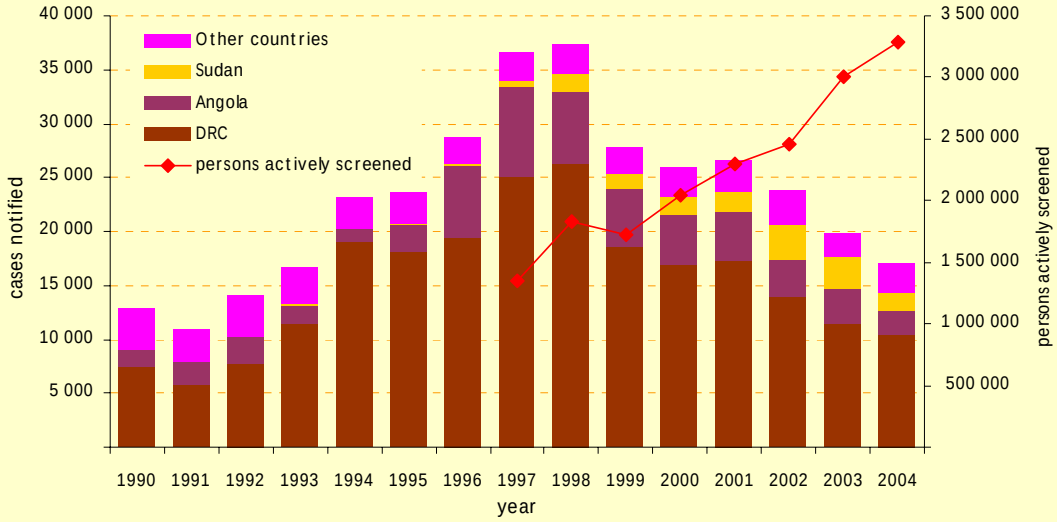
The 2001 agreement runs out this year and WHO and sanofi-aventis are negotiating an extension of the contract. One of the key objectives for the coming years will be to increase the use of eflornithine by national treatment programmes. It is also expected that the new donation will include provisions to provide free infusion kits to facilitate the use of eflornithine and would primarily target selected national programmes.

2. Overview of the current situation

2.1. Global HAT epidemiology: what are the latest trends?

Worldwide, **17,036** *T.b.gambiense* **cases were notified to WHO in 2004** (of which 10,369 or 60.9% in the DRC, 2,280 in Angola, 1,766 in southern Sudan, 859 in the RoC, 737 in the CAR, and 354 in Uganda). This is down significantly 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 3 million actively screened per year in 2003 and 2004 (Figure 2).

Figure 2. Yearly trends in number of *T.b.gambiense* cases notified throughout Africa, and total number of persons screened actively, 1990-2004[1]



2.1.1. Help arrives to 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.

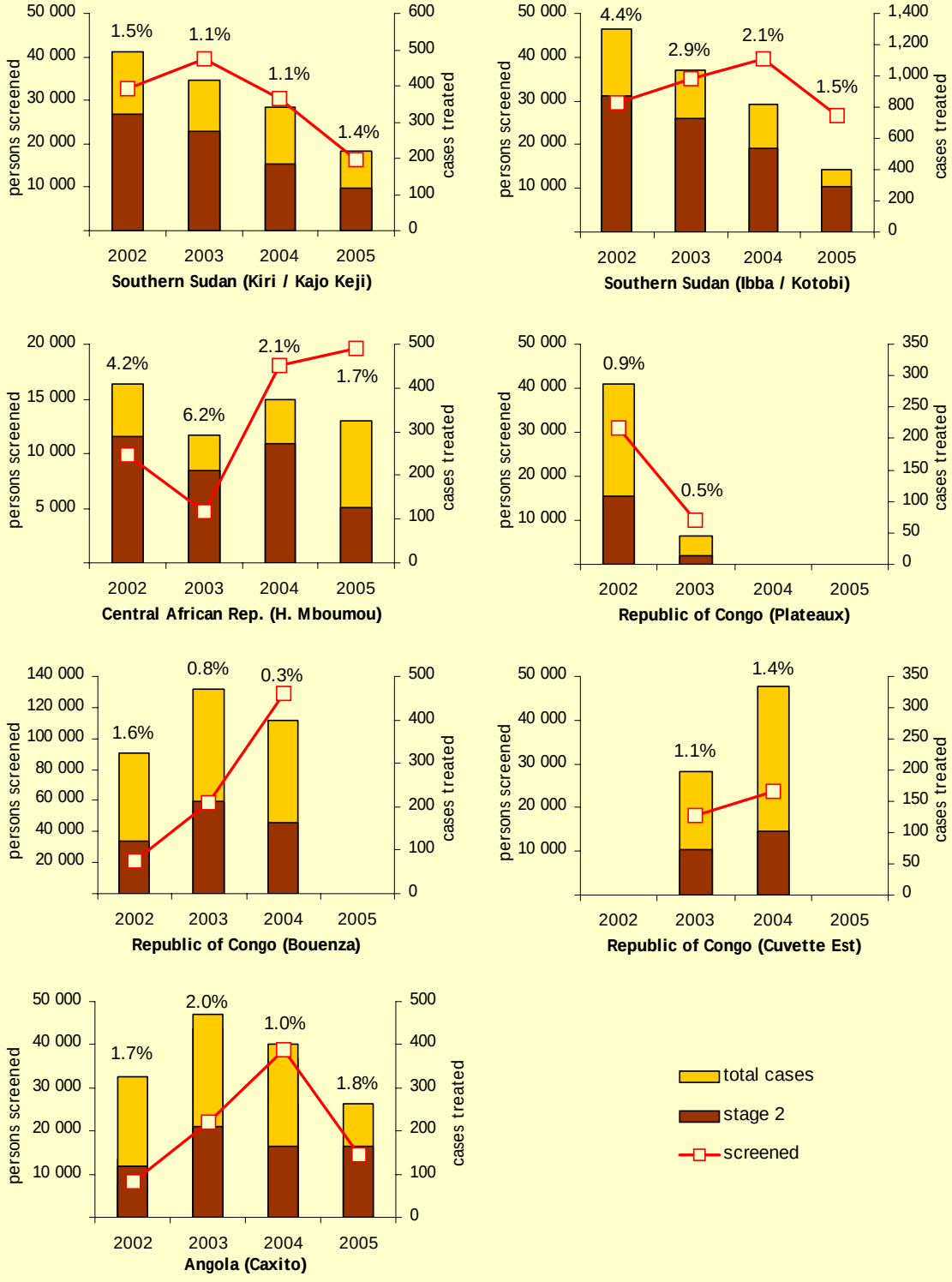
	2003		2004		2005	
	n	%	n	%	n	%
Total screened	187,721		297,000		196,746	
Stage 1 treated	1,102	38.1	1,260	41.0	1,455	52.0
Stage 2 treated	1,724	59.5	1,782	58.0	1,227	43.9
Total treated	2,896		3,075		2,796	

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. 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 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 the 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 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 Malange and Uige (<5%) and highest in Zaire (21%) 1998 comparison[5]: 154,700 screened, 6,610 cases (prevalence 4.3%)	Endemic provinces: - Bengo (MSF-Belgium, ICCT†) - Kuanza Norte (ICCT, Belgian Coop., MSF-France) - Kuanza Sul (ICCT) - Malange (ICCT) - Uige (ICCT, Caritas/Angotrip, Belgian Coop.) - Zaire (ICCT, Belgian Coop.) - Luanda (ICCT) † National Programme
Central African Republic	
Total: 737 cases - Haut Mboumou: 332 (prevalence 0.9% to 1.9%) - Ouham: 351 - Nola: 10 - Lobaye: 9 1998 comparison: 1,068	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	
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, low screening capacity.

Southern Sudan (no overall country 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 prevalences <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) - Mundri (Merlin plans intervention) - Yei (Malteser) - Kajo-Keji (MSF-Switzerland) - Mundri (Merlin plans intervention)

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

2.1.2. The problem of surveillance

In 2001, it was estimated that **only 6% of the population living in tsetse-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. **The coverage of screening remains low compared to the stated at-risk population** (8.9% in Angola, 17.6% in the DRC). Areas with 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 over-estimation, since it is merely based on proximity to tsetse breeding sites. However, in the absence of a specific test, 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 in 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**.

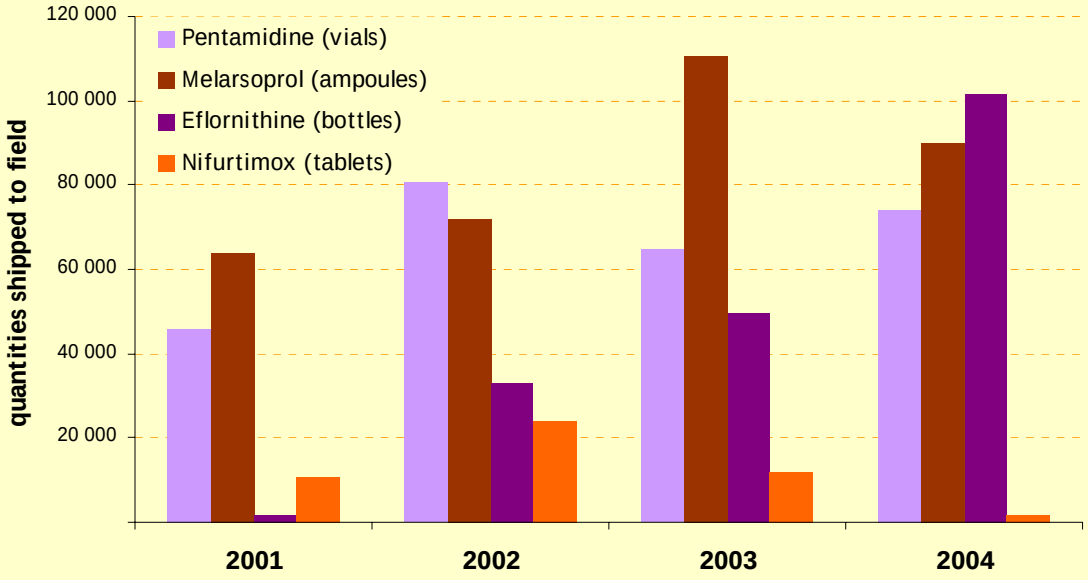
2.2 Four years of drug donations

2.2.1 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 fifty-fold from a mere 1,908 bottles in 2001 to

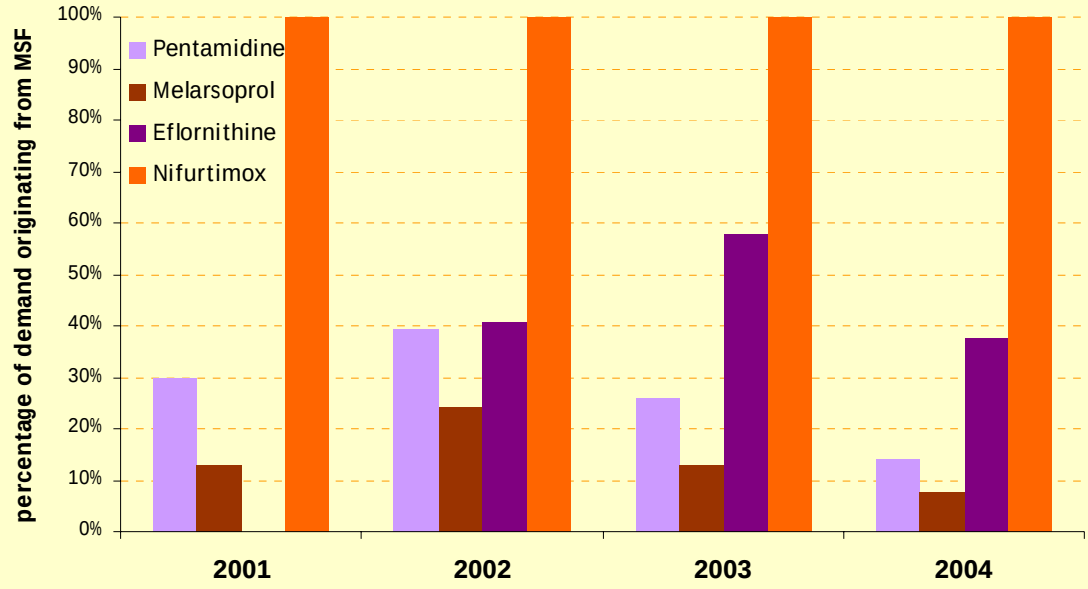
101,760 bottles in 2004. This is counterbalanced by a decline in melarsoprol shipments from 2003 (100,450 ampoules) to 2004 (90,100 ampoules). This decline could partially be explained by a decreased need for second-line treatments as a result of the deployment of eflornithine as effective first-line treatment in foci characterised by melarsoprol resistance, and where sufficient capacity exists to administer eflornithine. It may also reflect reluctance to use this drug, 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 3-5 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.

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)

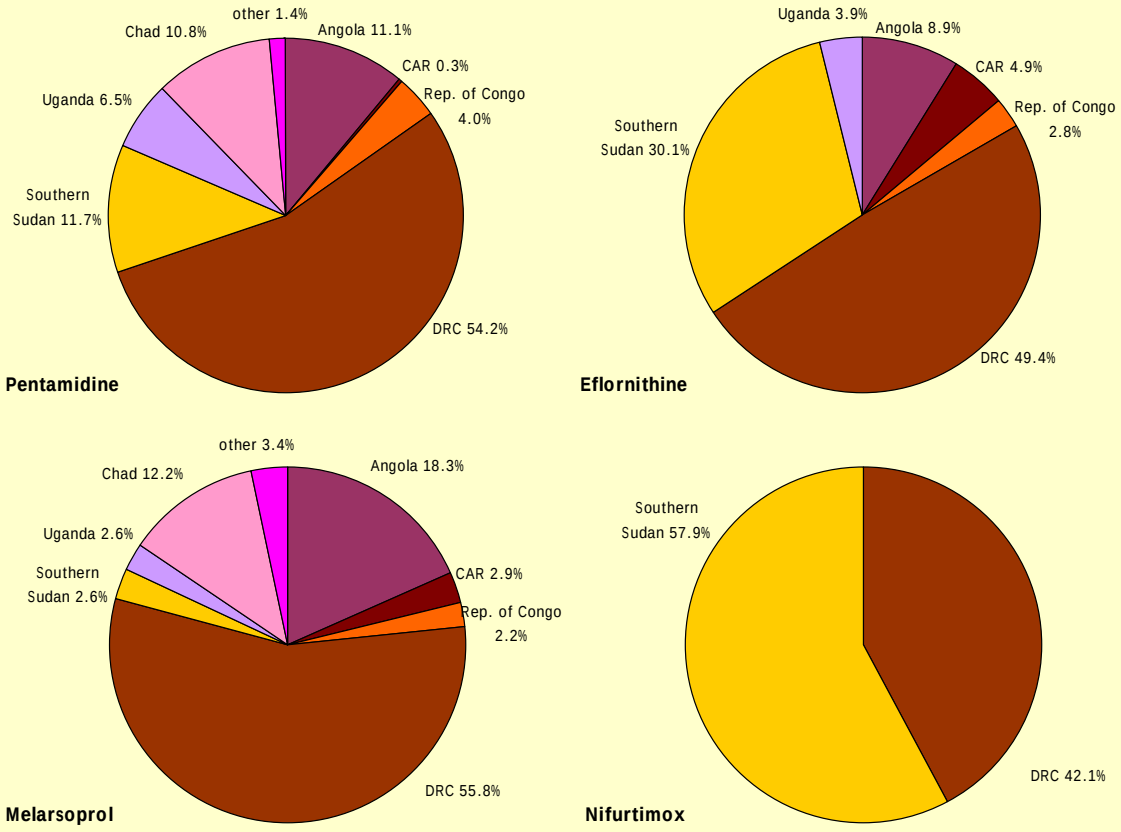


Source: MSF-Logistique

There appears to be a decline over the last three years in the demand originating from MSF (Figure 5), probably reflecting increased treatment capacity of other agencies, especially in Angola (10,000 melarsoprol ampoules ordered in 2002 vs. 16,500 in 2004) and the 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 for Chagas disease in the Americas).

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

Figure 6. Proportion of demand by destination country of shipment for the year 2004



Source: MSF-Logistique

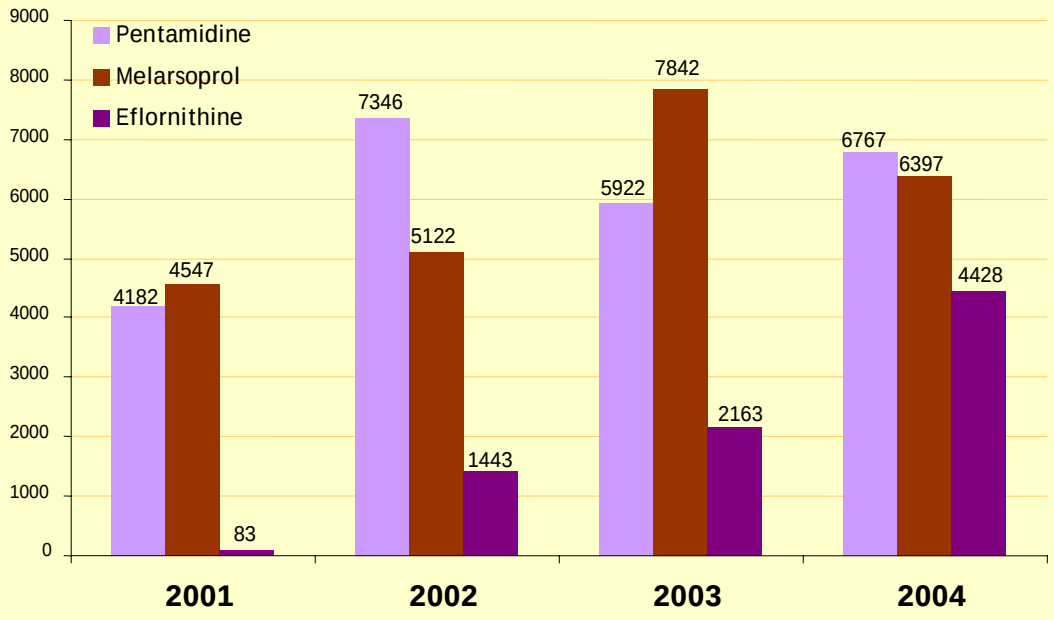
A *very rough* estimation of what these orders signify in terms of number of first-line treatments is provided below, based on standard treatment regimens described by the WHO[21]. Estimations were based on the following assumptions:

- Children under 15 years 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 of three days regimen;
- Drug wastage is 40% (estimated based a comparison of cases actually treated and quantities ordered in MSF programmes; source: Annick Hamel, MSF-France, pers. comm.).

As shown in Figure 7, stage 2 treatments are increasingly eflornithine-based. Every year, roughly around 6,800 gambiense stage 1 treatments (pentamidine only) may be administered. Assuming that stage 1 diagnoses are only 40% of 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 notified to WHO in 2004, and may thus be a reasonable proxy of actual treatment output.

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



2.2.2. MSF field experience with eflornithine

MSF has taken the lead in adopting eflornithine as first-line therapy replacing melarsoprol, introducing it in its field programmes in Uganda (now handed over to the Ministry of Health), Southern Sudan, CAR, RoC, and Angola. Evaluating effectiveness means checking patients at the mandatory 6, 12, 18 and 24-month follow-up visits for relapsing parasites. **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 under treatment (mostly of HAT-related complications), compared to the usual 5% or more under 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 ten-day melarsoprol.[22] The risk of death under eflornithine treatment was thus one fifth that under melarsoprol. 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, Angola and the RoC are currently under analysis or in press. Preliminary results, however, are promising: out of 249 patients followed for 12 months in Kajo Keji, only 3.6% experienced a relapse[22], whereas in nearby Ibba/Kotobi, the 24-month relapse rate among 2,094 patients was 6.8% (MSF-France unpublished data), comparing very 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, twenty-four hour nursing care and medical supervision. It should be noted however that the overall benefit to the patients outweigh these difficulties. Even though drugs may be free, perfusion materials (bottles, fluid, catheters, needles) increase the cost.

2.3. Issues with diagnosis

2.3.1. Ideal qualities of a test for HAT

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 of a HAT test are therefore:

- high sensitivity[†] (>99%), since HAT is fatal unless treated;
- high specificity (>99%), since HAT treatments are costly and toxic;
- classifies patient 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;
- equally accurate irrespective of trypanosome strain;
- yields reproducible results provided a minimal level of technician training;
- can be used to monitor the outcome of treatment over time;
- feasible in remote settings where mass screening is carried out;
- does not require a cold chain;
- yields an immediate result;
- safe and acceptable to the patient; ideally does not require cerebro-spinal fluid (CSF), lymphatic fluid or blood samples;
- 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 (see below).

2.3.2. 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 test alone 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 .[23]

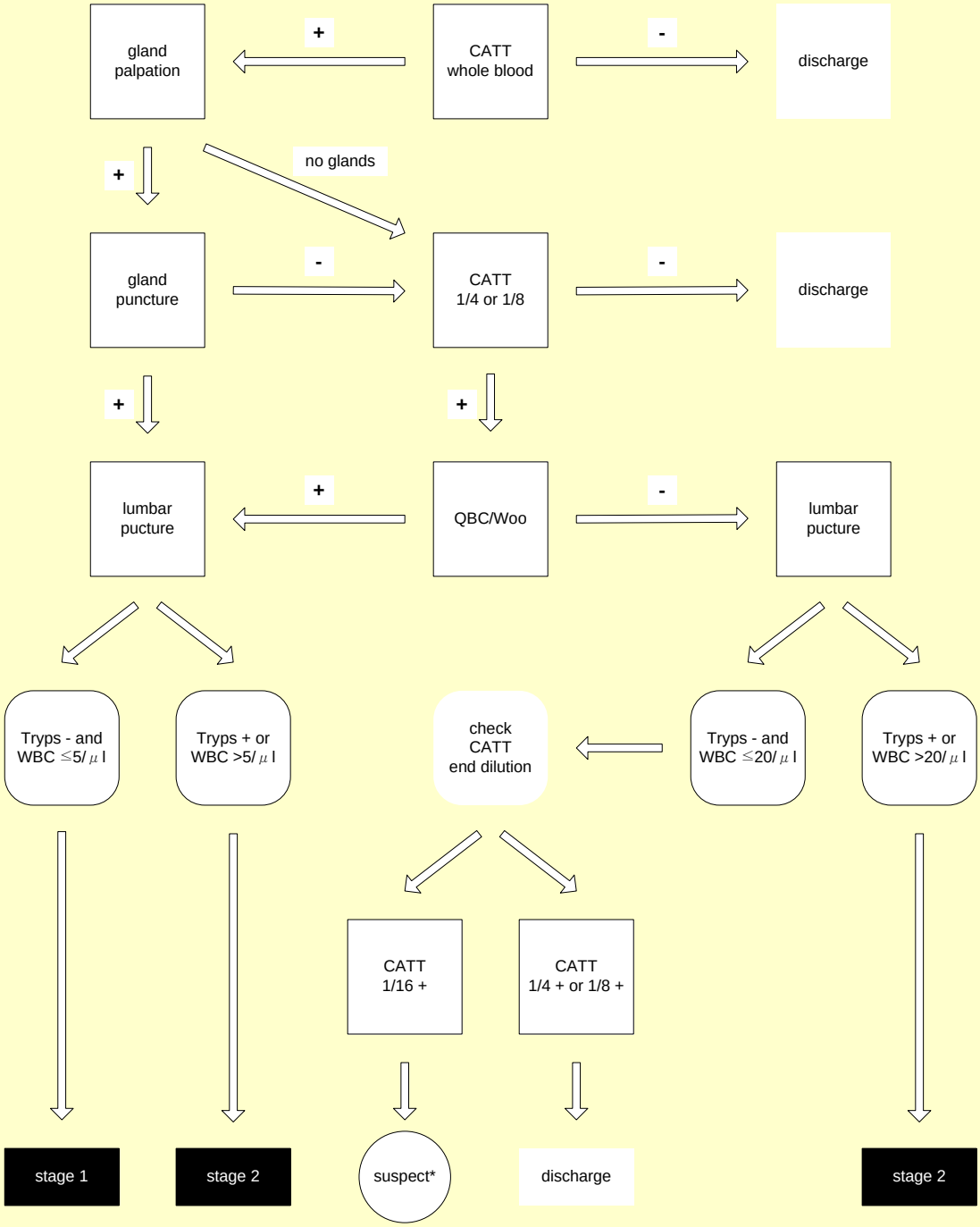
There are essentially three steps to diagnosis of HAT:

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 specificity (around 95%). 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

[†] *Sensitivity* is the extent to which the test is able detect positive cases (thus, a very sensitive test misses very few cases). *Specificity* is the ability of the test to only detect the truly positive cases (thus, a poorly specific test yields many false positive results). So as 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*.

apparatus to perform the test costs $US 398 (source: Eddie Magnus, Institut de Médecine Tropicale, Antwerp).

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



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

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 on the field are[23]:

- microscopic observation of fluid aspirated from the lymphatic glands of patients who display these 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:
    - 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;
    - mini-anion exchange column technique (mAECT); developed by the Institut de Médecine Tropicale (IMT) and currently produced in Kinshasa. This chromatographic tool achieves a sensitivity that is better than the Woo test and comparable the QBC test.[24] However, it is more laborious and expensive than other blood detection techniques. A joint IMT and MSF-Belgium study evaluating mAECT use in the field is currently underway in Angola.

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 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 less 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 (see below). Patients with WBC counts of 6-19 WBC/µL are sometimes considered 'intermediate stage', and, in Angola, receive pentamidine.

Among the major constraints of current HAT diagnostic tools are that:

- human resources (laboratory technicians) must be highly skilled in the various techniques;
- electricity is necessary;
- parasitological confirmation and staging is difficult to perform at the mass screening/community level;
- a variety of tests, testing kits, reagents and spare parts must be kept in stock, thus complicating programme logistics;
- the amount of tests employed makes quality control difficult to implement;
- 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 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;
- lumbar puncture is difficult to perform and very painful for patients;
- the threshold of detection of parasite density is too high, thus leading to under-detection of individuals with low parasite density;

- 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 diagnostic tests is not fully ensured. The CATT test is manufactured only by the Institut de Médecine Tropicale (IMT) 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 in Africa has not been successful. Nevertheless, IMT staff are confident that capacity can keep up with needs (production has been increased over the years from around 300,000 tests in 1987 to almost 3,000,000 in 2004; source: Eddie Magnus, IMT).

Despite the fact that it is more sensitive to low parasite densities than the Woo test and that it is appreciated by laboratory staff[23], the QBC test kit is no longer manufactured by Becton-Dickinson, and is therefore being progressively eliminated from diagnostic algorithms.

3. Perspectives for the future

3.1 Epidemiological evolution: can we predict future needs?

3.1.1 The decline may continue, but a reversal is possible

Even though HAT may be on the decline now, this trend can easily be reversed 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 in the CAR, and 7 in Cameroon.[18]

One of the paradoxes of HAT is that limited but thorough **control today is necessary, not only 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, TB, 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 programs to an integrated health care approach whereby diagnosis and treatment takes places within the day-to-day activities of a basic health care programme. This will require diagnostic and therapeutic advances.

3.1.2 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 Nigeria[25] and central Uganda,[26] 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 the 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 the above cases, were not related to armed conflict or displacement. Changes in land use patterns can favour tsetse reproduction or bring humans and flies in closer contact (a good example is the conversion of natural environments into plantations, as was done in the Ivory Coast).[27] Migration and travel for economic or other reasons could also contribute to creating new foci.

Interestingly, war and conflict has had no impact on HAT epidemiology in West Africa, whereas armed conflict, directly or indirectly, led to the vast epidemics of HAT 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 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.

3.1.3 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. 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 gambiense trypanosomes, and that some species, notably wild antelopes and reared pigs, are particularly susceptible.[28] 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 in the human population from animal reservoirs.[29]

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, even 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[30] and Cameroon.[19] 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 has been active, and 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.**

3.1.4 Which drugs will be most needed?

Key characteristics of an ideal drug for HAT (in addition to high efficacy and low toxicity) are:

- 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 by far preferred over intravenous;
- the ability to efficiently cross the blood-brain barrier, as well as be active against the 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;
- affordable, appropriate and accessible;
- 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 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 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 (see below) 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, scarcity of adequate clinical study sites, and long patient recruitment and follow-up periods.

3.2.1 Progress in development of diagnostic tests

Research into new or improved diagnostic tools for HAT has been greatly limited by a scarcity of funds. Recently, a large proposal for a broad consortium effort to develop new tests for screening and diagnosis, stage confirmation and patient follow-up, as well as a reference gold standard test for clinical research, will be funded by 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 IMT, 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 IMT 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], interleukin-10 as a marker of stage 2, and the Loop-Mediated Isothermal Amplification (LAMP). These methods, however, are very sophisticated for now and may not have an application in routine field HAT programmes.

3.2.2. Evaluation of improved regimens using available drugs

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 while 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 lengthening the odds of resistance developing and suppressing strains resistant to either 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 is likely to enter the market for the next 8 to 10 years (see below). 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 dosage and duration of treatment (and thus cost, hospitalisation time, and toxicity) and improve overall cure rates. The two currently most important research efforts 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 a small MSF/Epicentre case series in Uganda (48 patients), which suggested a ten-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 seven-day, twice-daily eflornithine and ten-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) is being done in several sites: one has been started by MSF in 2004 in the RoC; three more sites supported by DNDi in the DRC, started July 2005. In addition, TDR is supporting this study in a third and fourth sites in Uganda. Taken together, the results of these 6 sites should provide the evidence base on the safety and efficacy of this new treatment protocol, and form the basis for a WHO-recommendation for the use of nifurtimox in HAT.

To date, 103 patients have been recruited in Nkayi, RoC, and randomised to either 14-day eflornithine (control arm) or eflornithine+nifurtimox treatment. Although follow up of the patients is not yet completed, so far no relapses or fatalities have occurred in the combination arm, which are very promising preliminary results. The final analysis is expected in 2007, although preliminary safety and efficacy data from Nkayi will be published before then. **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 however, will still be far from an ideal solution for HAT**.**

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 insufficient absorption of the oral formulation and consequent 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. Currently, a new phase II study is being prepared in Chad so as to refine dosage. Because this study would if successful have to be followed by a larger phase III efficacy evaluation, it is unlikely that the WHO/TDR 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 at the Swiss Tropical Institute.

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 evidence exists to justify the use of the 7-day regimen. A WHO/TDR-supported trial of 3-day versus 7-day pentamidine implemented in the 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. A new WHO/TDR trial may start soon in Angola.

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

	Study sites (institutions)	Rationale	Safety results	Efficacy results
Mono-therapies				
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]	High (7% relapses), equivalent to longer regimen[35,36]
Oral eflornithine (phase II dose-finding)	Ivory Coast (WHO/TDR)	far easier to administer than IV: less 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 so far insufficient for registration	low (up to 37% relapse rate)[37]; insufficient evidence[38]
Combination therapies				
Melarsoprol + nifurtimox	DRC (IMT Antwerp) Uganda case series (Epicentre)	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 case series (Epicentre)	as above	may be toxic (1/19 patients), treatment interruptions[39]	DRC: 7% relapses as second-line[40] Uganda: 0 relapses (18 patients)[39]
Eflornithine + nifurtimox	Case series: Uganda Multi-centric trial ongoing: RoC, DRC (MSF/Epicentre/DNDi) Angola, DRC, Uganda (Epicentre, STI, PNLTHA, ICCT, NSSCP, WHO/TDR, DNDi)	as above; protect eflornithine against resistance and simplify regimen	Preliminary findings: low toxicity , few treatment interruptions[39]	Uganda case series: 0 relapses(48 patients)[39] Comparative trials: ongoing (encouraging results, first analysis 2007)

3.2.3 Finding new producers for 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 raw material for eflornithine is currently being done by Scinopharm (Taiwan). On the other hand, melarsoprol manufacture is likely to remain within sanofi-aventis, since it is perceived that this drug is obsolete, and due to concerns about availability of the raw material and complexity of 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.

3.2.4 Development of new drugs

Compared to the last fifteen years, there is currently a revival of HAT drug 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 that **a single HAT drug trial could take as long as four-five years from conception to reporting, and the entire process of development could take at least 10 years**. Shortcuts are, however, possible if a drug that has been developed and/or registered for a different disease is found to also have trypanocidal properties.

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

Drug / project	Sponsors / leading institutions	Phase of research	Notes
pafuramidine maleate (DB289)	Gates Consortium (UNC-Chapel Hill, STI, Immtech)	Phase III trial about to start: final results for registration could be available by 2007-2008	10-day , twice-daily oral regimen, for stage 1 only; fear of resistance / melarsoprol cross-resistance
DB844	Gates Consortium	Animal models (potential registration no earlier than 2013)	for stage 1/2; fear of resistance / melarsoprol cross-resistance
Nitro-imidazoles	DNDi	Exploration; could have some candidates by 2006-7	Could offer crucial shortcut in development by identifying drugs already registered for other diseases (mostly opportunistic infections)
Crossing of blood-brain barrier	DNDi	Discovery phase	Investigating pharmacological strategies to improve passage of blood-brain barrier by HAT drugs
Identification of other potential candidates		Ongoing; discovery phase	Hundreds of compounds from different sources to be screened

Presently, only one compound (formerly DB289, recently re-named pafuramidine maleate) has reached the field efficacy testing (phase III) phase, and it is only useful for stage 1. A 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 5 to 10 days. A Phase III trial is being prepared in six to seven sites (in the DRC, Angola, and southern Sudan) under the coordination of the Swiss Tropical Institute.

As for stage 2, the best prospects lie with the candidate drug DB844, which has shown encouraging results in animals. This drug is however 5 years away from field testing in the base-case scenario, with no 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, 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 testing**. Out of these, it is to be expected that fewer still (if any) will prove sufficiently safe and efficacious for human 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 1 clinical (pafuramidine maleate) and 1 discovery candidate (DB844), the best prospects for new treatments probably lie with the Drugs for Neglected Diseases initiative (DNDi) which, in addition to providing much-needed funding for HAT, has taken on a very important role of revitalising, coordinating, and creating links between different research efforts.

4. Recommendations

4.1. Encouraging progress, 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) amount of funding and institutional commitment to control the disease;
- larger number of actors interested in the disease, including NGOs, leading to better coverage of active foci;
- end of armed conflict in most of the active foci, leading to better access of treatment agencies to patients and of patients to treatment centres;
- availability of relatively efficacious, though difficult-to-administer drugs (eflornithine) from a well-managed, accessible stock, provided that the present donation agreements are renewed;
- increased local human resources capacity;
- 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 (this point however hinges on continued reliance on vertical programmes);
- relatively well-funded, high-level research into new 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 most important of these are summarised in Table 7.

4.2. Covering the research gap: why donation agreements must be renewed

The WHO-sanofi-aventis agreement to provide free pentamidine, melarsoprol, and eflornithine will expire in May 2006, at a period when demand for these drugs (and especially for eflornithine) has increased at a steady pace. The donation agreement looks set for a renewal according to sanofi-aventis and WHO. The terms and duration of the new donation are yet to be revealed, but the new contract is likely to last five years, and sanofi-aventis will continue to honour its three-pronged commitment to production, availability, and donation of HAT drugs. In addition, the company will accept liability for drug quality. HAT has recently been included in a list of diseases targeted by sanofi-aventis' "Policy of Access to Medicines in the 'Southern Countries'", raising hopes that the company intends to prolong its commitment to free drug donations.[41]

The WHO-Bayer agreement, at least as far as nifurtimox use in HAT is concerned, survives amid perils thanks to a stratagem of combining research with compassionate use. While the company balks at the idea of its product being used to treat HAT patients without formal registration or an official recommendation, control agencies and academia have so far offered unsatisfactory solutions to make nifurtimox available to patients for as long as needed. 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 within the next five years, and that not using eflornithine in this combination would entail a high risk of losing the most important HAT drug to resistance with no certain prospect for a replacement (the same logic applies to nifurtimox if used in monotherapy).

Table 7. Main probable threats to sustained HAT control over the next decade.

Threat	Potential implications
Perception that HAT is no longer a serious problem	Funding more difficult to obtain, reduced commitment for control and research: risk of neglect leading to new epidemics
Agencies based in the North disengage from HAT control	National programmes less effective at lobbying for drug availability, increased research
Perception that drugs will be donated indefinitely	Less stimulus for development of new drugs, technology transfer to new producers; control programmes come to rely on donations
Highly skilled staff diverted to other programmes or depleted because of brain drain and HIV/AIDS epidemic	Lack of local human resources to implement HAT programmes; decrease in quality and capacity of national HAT programmes
Unsustainability of vertical programmes	Handover of NGOs to some national health authorities without clear provisions for funding and technical support
Changes in climate and land use	Expansion of tsetse habitats, increased likelihood of human-fly contact
Renewed armed conflict	Interruption of control efforts and research; increased human susceptibility, creation of new foci through population displacement
Development of eflornithine resistance	No more effective, non-toxic first- and second-line treatments (see Figure)
Nifurtimox not authorised for use in the next 5 years	Use of eflornithine in monotherapy with consequent risk of resistance development (see Figure)
Eflornithine + nifurtimox trials incomplete or inconclusive	Use of eflornithine in monotherapy (see Figure)
New production of HAT drugs is unsustainable	New producers discontinue production, leaving no other avenues for HAT drug supply (it is likely that sanofi-aventis and Bayer would be reluctant to resume production after technology transfer)
No new HAT drugs developed in the next 10 years	No effective alternative in case of eflornithine resistance or drug non-availability
Simplified diagnostic tests do not become available in the next 5 years	HAT services cannot be integrated into routine care, or poorly sensitive and specific diagnostic tools are used

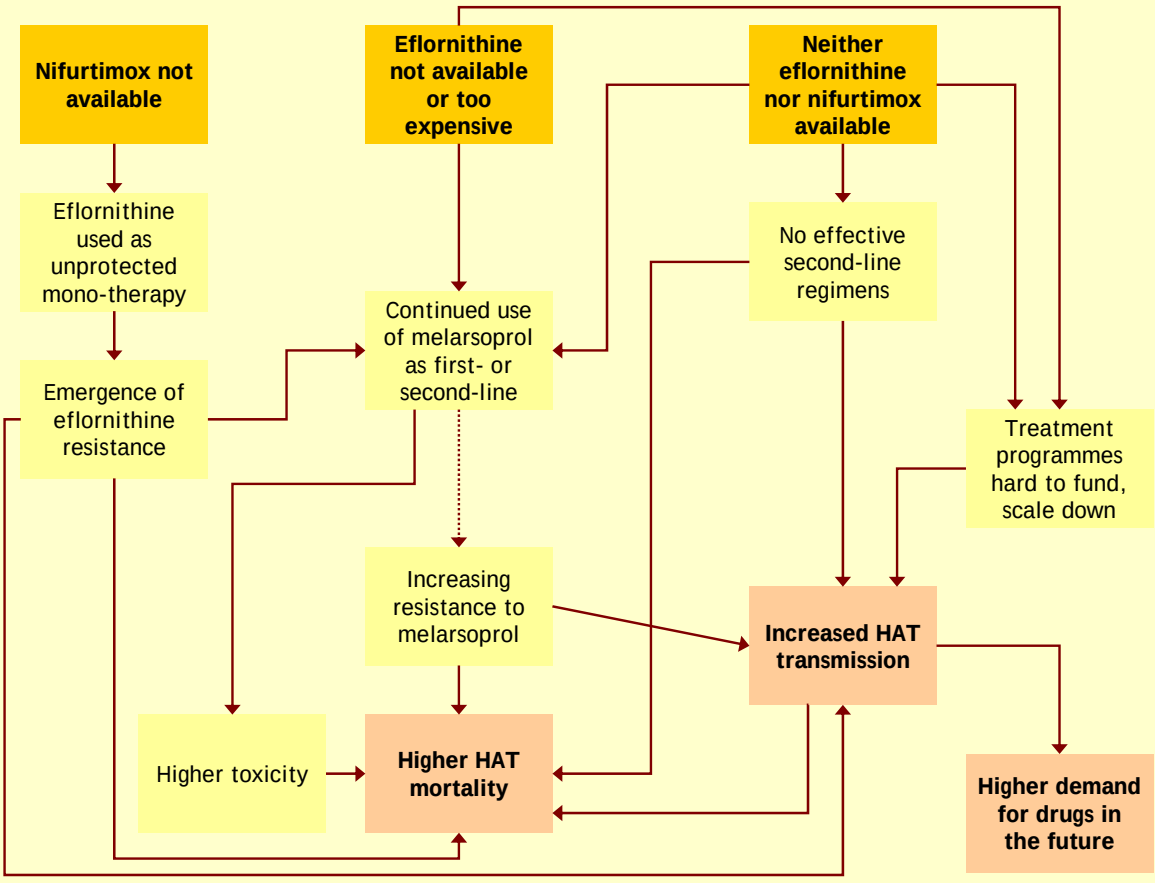
Given the sometimes frustratingly slow pace at which HAT policy develops, **it is not too early to prepare for what lies beyond the sanofi-aventis and Bayer agreements. There are several compelling reasons why both should be renewed and strengthened:**

- HAT continues to affect the poorest of the poor in the African continent; the drug which will increasingly be used to treat stage 2 (or about half of all cases), eflornithine, is far too expensive for patients and for national treatment agencies.
- If left untreated, HAT is an invariably fatal disease.
- HAT is already among the most neglected diseases and most treatment programmes are fragile; making these programmes pay for drugs might shrink resources for population screening. Alternatively, cost-recovery schemes might be put in place which would greatly reduce access to treatment and discourage stage 1 cases from seeking care early.
- Melarsoprol's usefulness is waning fast due to increasing treatment failures; in addition, emerging data showing that eflornithine is safer and more efficacious will soon make first-line use of melarosprol ethically unjustifiable unless insurmountable logistical constraints impede the administration of iv eflornithine. Eflornithine is therefore quickly becoming an essential drug.
- Eflornithine+nifurtimox may well become the recommended first-line treatment for HAT within the next five years; nifurtimox is thus a necessary, irreplaceable partner drug for eflornithine.

- Providing free HAT drugs is currently key to expanding treatment coverage, thus reducing the human reservoir of HAT and keeping the risk of new epidemics low.
- A centralised, well managed stock is necessary to manage limited resources efficiently, make orders and delivery swift, and concentrate data on HAT drug use, thus providing an entry point for effective surveillance of trends in treatment output.

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 expected effects of non-availability of eflornithine, nifurtimox, or both.



4.3. A sustainable future: new tools badly needed

The sanofi-aventis and Bayer donation agreements should be viewed as a temporary measure, while development of new drugs is completed, assuming that these will be affordable. Vertical drug donation programmes form the bulk of the pharmaceutical industry's response to the crisis in the treatment of neglected tropical diseases.[42] However, many of these programmes do not offer, and sometimes prevent, sustainable solutions.[43] In the case of HAT, the sanofi-aventis and Bayer donations:

- Impede thoughtful planning over the long-term, since they are time-bound (five years for sanofi-aventis, one to two years for Bayer), and since there is no written commitment on the part of both manufacturers to maintain production of all HAT drugs for as long as there is need; in such a climate, WHO's stated goal to eliminate HAT appears irrelevant.

- May create complacency among donors and treatment agencies about the drugs' gratuity.
- Could discourage other commercial manufacturers from becoming involved in HAT research.

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 search for new effective and affordable drugs.

While the development of 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 safe, and has not been compromised by parasite resistance in over fifty 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 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 2013-2015. As there is no guarantee that this will indeed occur, the development and registration of eflornithine+nifurtimox could not be more urgent.

Progress in HAT diagnostics research is even slower and less well-funded than that for treatment. The most pressing needs continue to be for a highly sensitive, specific and simple screening, confirmatory test (possibly based on serology), and an accurate, possibly non-invasive test to determine stage.

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.

4.4. What is the role of MSF?

Today, MSF accounts for around one fifth of the total number of patients being diagnosed and treated. More importantly, the organisation is currently entirely responsible for efficient supply and distribution of all HAT drugs. In association with Epicentre, it is currently implementing the most crucial study of HAT treatment in years (the NECT trial of eflornithine+nifurtimox). MSF is also a prime donor and driving force behind the 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 the most authoritative and vocal advocate 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 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 a disease that will soon fall off the agenda of international donors and national programmes.

4.5 Recommendations

4.5.1 To MSF Access Campaign, operations and medical departments

MSF programmes will increasingly be faced with the dilemma of how to hand over programmes that, due to their logistical complication (necessary for eflornithine administration and intensity of active screening), rely heavily on international staff for supervision of clinical and laboratory work, and have significant cost inputs (for example to equip inpatient facilities capable of administering perfusions). Such programmes are unlikely to be replicated by national control agencies.

Once epidemics die down, HAT control stands a better chance of being sustainable if integrated into routine primary and secondary health care services. This integration is nearly impossible today because of the complexity of drug regimens and diagnostics. In line with its approach towards other diseases such as malaria, HIV/AIDS, kala azar and meningitis, **MSF needs to invest more resources in (promoting) research and development**, so that new and improved therapeutic and diagnostic tools become available which can successfully be deployed in routine health care. MSF's role in field evaluation and validation of these tools should be fostered.

Finally, MSF (and other agencies) mode of delivering HAT diagnosis and treatment should change from the traditional approach of vertical, epidemic-geared programmes; instead, new cost-effective and easy-to-maintain models for controlling HAT in residually active foci must be developed.

Specific recommendations include:

1. Continuing to support DNDi's efforts in HAT drug research.
2. Supporting operational research in the fields of diagnostics (new tools) and treatments in MSF HAT control programme sites, and properly documenting and publishing or otherwise disseminating the results.
3. Organising better follow-up of any patients treated with nifurtimox outside of NECT trial, according to information needs suggested by TDR so as to facilitate a WHO recommendation for use of the drug.
4. Exploring ways to resume production of the QBC diagnostic kits. A temporary resumption of production (for example, enough to re-supply agencies for the next 15 years, while new-generation tests come on the market) would perhaps be sufficient.
5. Publishing eflornithine efficacy and safety data as soon as possible in peer-reviewed journals, preferably high-impact and open access for the developing world. It is difficult to argue in favour of making this drug available with unpublished data.
6. Being more pro-active in describing and representing the needs of patients and field programmes (e.g. specifications of drugs and tests most likely to be feasible and effective in field practice).
7. Participating in the renegotiation of the donation agreements by advocating simultaneously for an extension of the donation and a renewed effort to find willing producers for HAT drugs. The two processes cannot be separated, and the donations are an acceptable solution only insofar as they help to bridge the gap while new producers are found and new drugs are developed. Advocating for non-time-bound donations may be more strategic.
8. Intensifying the search for alternative HAT drug producers, focussing in particular on eflornithine and nifurtimox.
9. Liaising more effectively with other treatment agencies and WHO in order to obtain a better overview of continent-wide trends in HAT epidemiology, coverage of needs, and treatment protocols. This will also help to identify other HAT foci where MSF's intervention may be warranted. In general, WHO should be encouraged to collect more comprehensive data on HAT epidemiology, and above all make these data public.

10. Exploring new, creative ways to expand active screening activities whilst improving the efficiency (or ratio of persons screened per new case detected) of screening campaigns. MSF's deployment of mobile country-wide screening teams in the RoC is one such example.
11. Developing new operational strategies to diagnose and treat HAT patients in low-prevalence areas. This requires a move away from expensive vertical programs to a more integrated approach to diagnosis and treatment.

4.5.2 To parties involved in negotiating new donation agreements

1. Negotiate new agreements that are not time bound, or at least offer HAT drugs for a period sufficiently long to enable proper planning (e.g. 15 years) or until affordable versions of the present drugs are available from new producers.
2. Explore ways to increase the use of eflornithine in national programmes through the provision of infusion kits and through increasing capacity of health workers to manage patients.
3. Ensure production and availability of nifurtimox for governmental and non-governmental agencies for use on a compassionate basis as well as for use in combinations in pilot programmes.
4. Obtain a written commitment from Bayer AG that the production of this drug will not cease.

4.5.3. Some suggestions for further research

1. The ongoing development of eflornithine+nifurtimox as an alternative regimen for stage 2 HAT should be expedited as much as possible.
2. As relapses to eflornithine are already being noted, it is important to investigate these as soon as possible to ascertain whether they are likely to constitute true episodes of parasite resistance.
3. Some results from the DRC equivalence study of 3-day vs. 7-day pentamidine might perhaps yet be salvaged through late follow-up of trial participants. In general, studying the efficacy of this shorter regimen may be as important for stage 1 HAT as continuing the development of DB289.
4. a rapid CATT test
5. explore new bio-technology platforms that will enable non-invasive diagnosis and staging of the disease
6. Spatial epidemiology and mathematical modelling should be used to better quantify and predict the evolution of the burden of HAT disease. The most complete and updated figures on total population at risk per affected country are needed, and HAT incidence outside of areas under surveillance should be studied.

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