

Subsequently, disease endemic-countries decided in May 2006 to switch from the toxic organo-arsenic melarsoprol to the less toxic but cumbersome eflornithine, and requested WHO support. WHO developed an eflornithine administration kit which includes the drug as well as all solvents and equipment required (Annex 1) to allow countries to implement their national policy for HAT treatment and reduce as much as possible to number of HAT patients treated by the last organo-arsenic drug in use in the world. This allowed eflornithine, which previously was used almost exclusively by NGOs to be increasingly used by Sleeping Sickness National Control Programmes (Annex 2). This has largely contributed to the decrease in the use of melarsoprol for the treatment of second stage of *T.b.gambiense* (Annex 3)

WHO signed agreements with the manufacturers of all four available drugs for HAT: sanofi-aventis (pentamidine, melarsoprol and eflornithine) and Bayer HealthCare (suramin). It is expected that nifurtimox, which is produced by Bayer HealthCare, will be included in the donation agreement. These agreements provided for these drugs to be donated to WHO and distributed to disease-endemic countries free of charge (Annex 4).

The inclusion of nifurtimox+eflornithine combination for the treatment of *T.b.gambiense* second stage in the Essential Medicines List

From the information provided above, it is obvious that an improvement of treatment of HAT, especially 2nd stage HAT, is urgently needed. WHO has supported and has been involved in all the initiatives for the research for new treatments which are safer, easier to use and/cheaper. Within this context, WHO has followed and supported the initiatives to evaluate the efficacy and safety of combinations of drugs versus monotherapy as potential alternative treatments to facilitate administration, reduce toxicity, increase efficacy and/or reduce the cost of the treatment. These initiatives included the combination of eflornithine with nifurtimox, a drug not approved for treatment of HAT, but approved for treatment of Chagas disease (American Trypanosomiasis) and for which pre-clinical data suggested that it might have efficacy against *Trypanosoma brucei gambiense*.

In October 2008, DNDi submitted to the WHO EML Committee a proposal to include the nifurtimox+eflornithine combination as treatment for stage 2 *Trypanosoma brucei gambiense* HAT in the WHO Model List of Essential Medicines. Both drugs are currently in the EML: Eflornithine as monotherapy for HAT and nifurtimox as monotherapy for American Trypanosomiasis.

This proposal is strongly supported by the results of a non-inferiority clinical trial comparing the nifurtimox+eflornithine combination with eflornithine monotherapy. Clinical trials to develop clinical products for HAT are very challenging and complicated¹. The nifurtimox+eflornithine combination study has been very closely followed by WHO, which supported all steps of the project, including supply of the drugs, visits to the study sites and attending clinical trial monitoring meetings. An independent audit confirmed that the study was performed according to Good Clinical Practice and with an adequate scientific quality. In this study, the non inferiority of the nifurtimox+eflornithine combination therapy versus eflornithine monotherapy (currently recommended treatment) has been demonstrated. (See proposal).

From the data from this trial, it is concluded that the introduction of nifurtimox+eflornithine combination therapy could result in many advantages in the management of cases of HAT:

¹ Recommendations of the informal consultation on issues for Clinical Product Development for Human African Trypanosomiasis. Geneva 9-10 September 2004. WHO 2007

1. *Improved access to eflornithine*

The treatment currently still used in 60-70% of the stage 2 HAT gambiense cases despite its toxicity is melarsoprol. The percentage of patients being treated with melarsoprol has remained that high despite the coordinated efforts of WHO and disease endemic countries to introduce eflornithine, as first line treatment. This is due to resource constraints limiting the speed of expansion of eflornithine use (need of sufficient qualified staff, need of an adequate distribution and logistic chain of transport).

The introduction of the combination will reduce many of these constraints and will allow a faster reduction in the percentage of patients who are treated with a very toxic drug when a safer treatment is available.

2. *Toxicity*

The reduced exposure to eflornithine of the combination treatment (7 days of 400 mg/kg/day) as compared with the standard eflornithine treatment schedule *14 days of 400 mg/kg/day) is expected to reduce the risk of bone marrow toxicity and the subsequent risk of sepsis in a very weak healthcare environment.

The reduced number of infusions is expected to result in less risk of catheter related infections.

3. *Treatment failures*

Based on the experience in other diseases (e.g. malaria, tuberculosis, leprosy and other bacterial diseases) the use of drug combinations will reduce the probability or slow down the emergence of resistance. Considering that only 2 drugs are currently approved to treat HAT and the extremely low level of research efforts focused on new drugs for HAT, the increase of the resistance levels already observed will leave many patients without treatment options for a lethal disease.

4. *Drug compliance*

The eflornithine-nifurtimox combination treatment requires infusions every 12 hours for 7 days as compared to infusions every 6 hours for 14 days required for the standard eflornithine treatment. Both the reduction of eflornithine infusions from 4 to 2 / day (and in particular no night time infusion) and the reduction in the number of days from 14 to 7 is expected to result in improved compliance. This increases the probability of cure and reduces the probability of emergence of resistance. In addition the combination treatment schedule significantly reduces the burden for the nursing staff (less perfusions to be prepared and controlled, less IV lines to be placed,...). This means a lower need for qualified staff, which is scarce in affected areas and shorter hospital stays and thus further decreases the cost of treatment.

Conclusion

The inclusion of the nifurtimox+eflornithine combination therapy in the EML will facilitate the implementation of WHO's policy on HAT *T.b. gambiense* second stage treatment and will make it easy to support the countries in the implementation of their national policies.

Therefore, the technical unit in Innovative and Intensified Disease Management in the Department of Control of Neglected Tropical Diseases supports the inclusion of nifurtimox and eflornithine combination for the treatment of *T.b.gambiense* second stage in the Essential Medicines List.

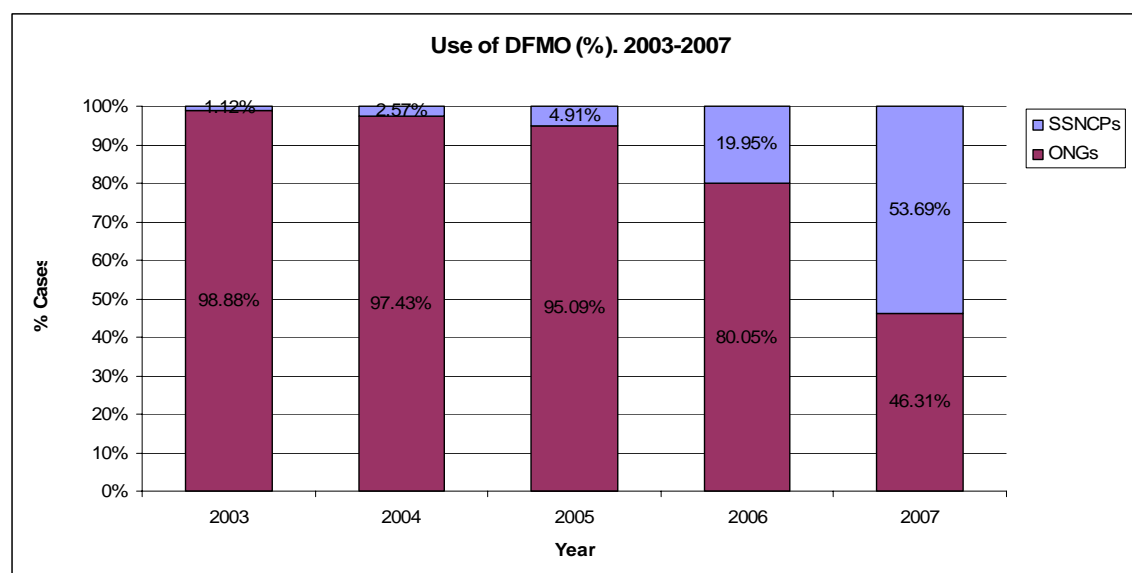
Annex 1:

Contents of the kit to administer two treatments of eflornithine -monotherapy

Item	Quantity
Eflornithine chlorhydrate, éq. 200 mg/ml base, 100 ml, ampoules	36
Other equipment:	
Water for injection, 100 ml, plastic pouch	120
'Y' joint, Luer lock, air intake, sterile	120
IV catheter, injection, 20 G (1.0 x 32 mm), pink	50
IV catheter, Bouchon, male Luer cap, sterile	100
Needle, Luer, 19G (1.1 x 40 mm) cream, IV	200
Syringe, u.u., Luer, 20 ml	100
Syringe, u.u., Luer, 2 ml	100
Strip of gauze, 8 cm x 4 m, with edges	20
Gauze pad, 10 cm, 12 ply, sterile	140
Zinc oxide tape, roll, perforated, 10 cm x 5 cm	1
Cotton, roll, 500 g	1
Examination gloves, latex, one-time usage, large	100
Examination gloves, latex, one-time usage, small	100
Povidone iodine, 10% solution, 200 ml vial for pouring	1
Elastic tourniquet 100 cm x 1.8 cm	2

Annex 2:

Rate of use eflornithine (DFMO) Sleeping Sickness Control Programmes versus NGOs



Annex 3:

Rate of drugs used as a first line to treat second stage *T.b. gambiense*

	2003	2004	2005	2006	2007
Patients stage 2	12249	10609	9826	7120	6461
Treated with melarsoprol	10179 (83.1%)	9088 (85.7%)	8204 (83.5%)	6287 (88.3%)	4393 (68%)
Treated with eflornithine	2058 (16.8%)	1515 (14.2%)	1609 (16.4%)	827 (11.6%)	2060 (31.9%)

Annex 4:

HAT drugs distributed by WHO. July 2001-July 2008

	Units (vials) supplied	Treatments supplied
Melarsoprol	536,449	59,605
Pentamidine	393,577	49,1974
Eflornithine	276,913	17,307
Suramin	24,530	4,088
	1,231,469	130,198

Annex 5:

Comparison between eflornithine+nifurtimox kit and the eflornithine monotherapy kit

Cost per treatment placed in Kinshasa (DRC) in euros

	Nifurtimox- Eflornithine	Eflornithine
Volume (dm ³)	25	85
Weight	9	19
Cost drugs THA	180	360
Cost solvent&equipment	43	87
Transport	6	22
Total	229	469