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Human African Trypanosomiasis

Treatment and Drug Resistance Network for Sleeping Sickness

Report of the Sixth Steering Committee Meeting 28-29 May 2002

Geneva, Switzerland

WORLD HEALTH ORGANISATION
Department of Communicable Diseases

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Introduction

The Sixth Steering Committee was held at WHO Headquarters in Geneva 28-29 May 2002.
The list of participants and Agenda are provided as Annex 1 and Annex 2.
The meeting was chaired by Dr R. Brun of the Swiss Tropical Institute (STI).

I General news from Surveillance and Control

WHA55: Technical Briefing for Elimination and for a global alliance

A technical briefing on African trypanosomiasis intensified control was held during the World Health Assembly on 15 May 2002.

WHA55: Resolution on PATTEC

Resolution to support PATTEC (presented by OAU) has been postponed to the next Executive Board and Assembly, mainly due to a controversy on the term eradication in the title of the resolution.

II The Working Group on drug availability and accessibility

- **Update on drug stocks**

	Amount to be delivered for year 1	Total drug received	Total drug distributed	Stock balance	% distributed on the first year supply
Eflornithine	60,000	58,618	41,925	16,693	69,8 %
Melarsoprol	315,000	547,500	92,713	454,787	26,4 %
Pentamidine	100,000	216,960	91,515	125,445	91,5 %
Suramin	10,000	9,705	1,505	8,200	15,5 %

A question was raise about the expiry date for melarsoprol which changed from 5 to 3 years only. Nobody was able to answer but the question will be raised in the next WHO/Aventis Collaborating Working Group to be held on 17 June 2002.

- **Forecasting for the next six months**

Eflornithine
The full supply for the first two years (120,000 vials) will be completed by 31 January 2003. About 70% of the first year supply has been distributed so far. A sufficient amount will be guaranteed to cover the needs for the next six months.

17,000 vials will be delivered in MSF Bordeaux around 15 July 2002
35,000 vials " " " " around 5 September 2002
60,000 vials " " " " around 31 January 2003

Melarsoprol
A total amount of 117,500 (17,7%) vials will be delivered by the end of the year to cover the planned amount (665,000 vials) for the first two years.
Only 30% of the first year stock has been distributed so far. The needs for the following 6 months will therefore be covered with no doubt.

Pentamidine
The supply for the first two years has been received and 16,960 vials have already been delivered for the third year. More than 90% of the first year delivery has been distributed so far.

Suramin
About 15,5 % of the delivery for the first year was distributed. The needs for the next six months will be covered with no problem.

- **Eflornithine use as a first line treatment**

It was recommended that countries should not use eflornithine as first line treatment as it should be used only in clinics that have the capacity of skilled, round-the-clock nursing care, and where high melarsoprol resistance is prevalent.
The MSF pilot experience ongoing in Ibba and Omugo should remain the only places where this treatment is used, as fatality cases have occurred and further reports are expected including on toxicity before any recommendation would be made.
Eflornithine used as first line treatment would be much more expensive than current schemes and would therefore reduce the proportion of cash in the Aventis donation available for research.
Eflornithine is already used for refractory cases like in Angola where 30% of cases are refractory ones. It should continue to be used to respond to treatment failure with melarsoprol.
The group shall wait for valuable information from MSF before further decision would be made.

III The Working Group on coordination of drug development and clinical trials

- **TDR's Strategic Direction for Research on HAT**

TDR's strategic research thrust for African trypanosomiasis places specific emphasis on basic knowledge and development of new drugs and diagnostics.

- **Megazol**

During a meeting held on 31 January 2002 with all partners involved in this project, it was decided to test the genotoxicity of this compound. The results will be available in mid-June. A meeting is planned to discuss results and plan the next steps.

- **Oral eflornithine**

Single centre, Phase II, PK trial, Daloa, Côte d'Ivoire on oral eflornithine
The pharmacokinetic study of oral eflornithine, comparing 2 doses (400mg/kg/day and 500 mg/kg/day) for 14 days took place in Côte d'Ivoire in 2001. Following a review of the results in June, it was recommended to carry out phase II trials.

Training of clinical investigators and monitors in GCP and members of Ethical Committees from Cote d'Ivoire and DRC in Ethics is being planned as a capacity building activity.

Multicentre, controlled clinical trial, four centers (DRC, Uganda) on abridged schedule for eflornithine (7 vs. 14 days). The results of this study are published in *WHO Bulletin* 2000, 78, 1283-1373.

- **Short-course pentamidine**

A single centre, controlled clinical trial on an abridged schedule for Pentamidine: 3 days vs. 7 days of 4 mg/kg, is ongoing at Bulwem in Mokala health zone, DRC .

- **Berenil**

TDR is considering if this compound, marketed for veterinary purposes, could be used in humans to treat early-stage HAT by oral route. An independent toxicologist reviewing the available safety dossier concluded that the dossier is acceptable for clinical trials.

- **Nifurtimox**

A WHO/Bayer meeting was held on 7 February 2002 to discuss several issues regarding Nifurtimox. Development of nifurtimox for the treatment of Melarsoprol-refractory HAT cases through label extension, is being considered.

- **Combination studies**

Single center, four arm trial on combination treatment, Bwamanda, DRC (Institute of Tropical Medicine-Antwerp)
Standard schedule for melarsoprol (3x3 3.6 mg/kg)
10 days melarsoprol (0.6 mg/kg, 1.2 mg/kg, 8 x 1.8 mg/kg)

Nifurtimox monotherapy 15 mg/kg 3xday, 14 days
Nifurtimox 15 mg/kg 2xday (8 days), melarsoprol, 0.6 mg/kg, 9 x 1.2 mg/kg (total 10 days)
The calculated patient number of 215 in each arm could not be achieved due to the onset of war activities. About 70 patients in each group could be included.
Main results:
The adapted short course for melarsoprol yielded higher relapse rate than the standard course.
Nifurtimox alone also yielded higher relapse rate.
Combination nifurtimox / melarsoprol did not show any relapse.
Publication in preparation.

Pentamidine in early Stage II HAT study (MSF/EPICENTRE)
A study on early stage II patients (up to 20 WBC in CSF) to test the efficacy of pentamidine vs. melarsoprol was carried out in Omugo, Uganda. The study had to be interrupted due to Ethical considerations, as the number of relapses in the Pentamidine arm was high. However, during the follow up the number of melarsoprol relapses made up and the overall results is now more equilibrated. The current rate reported is 44% for pentamidine, 33% for melarsoprol. Overall this rates are extremely high, contradicting previous reports of pentamidine efficacy in early cerebral stage, and coherent with the observed treatment failure rates with melarsoprol in the area. Treatment failures were defined as: presence of parasites in blood, lymph or CSF, increase in WBC counts in CSF, death during hospitalization or in the following month.

Single center, 3 arm controlled clinical trial, combination treatment, Omugo, Uganda
A trial on drug combinations was initiated as a consequence of the very high rate of relapses (25-30%) after melarsoprol treatment reported in Northern Uganda and Southern Sudan. The reasons for those relapses were discussed by the group (PK, P2 – transporter).
Due to the recent authorization by the Ugandan authorities for the use of eflornithine as the first line drug for second stage sleeping sickness (14 days for new cases, 7 days for relapse cases), plus high levels of toxicity and mortality observed in 2 of the arms, the trial was interrupted at an early stage. Recruitment has been very slow due to the decreasing number of patients in that area where a 6-year MSF programme has succeeded in lowering the prevalence.
Preliminary results
1. Melarsoprol (1.8 mg/kg 10 days / Nifurtimox 15 mg/kg 10 days) 17 treated, 4 casualties (24%), treatment interruption 22%
Main adverse effects reported in this group were diarrhea (44%), fever (39%), headache