



WHO/CDS/CSR/EDC/99.5

**Human African Trypanosomiasis Treatment and Drug
Resistance Network. Report of the first meeting.**

**Geneva, Switzerland
14-15 April 1999**

World Health Organization
Department of Communicable Disease Surveillance and
Response

This document has been downloaded from the WHO/CSR Web site. The original cover pages and lists of participants are not included. See <http://www.who.int/emc> for more information.

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Contents

	Page
1. Introduction.....	1
2. The Network	1
2.1 The Steering Committee.....	2
2.2 The Secretariat.....	2
2.3 The Working Groups.....	2
2.3.1 The Research Group	3
2.3.2 The Surveillance Group.....	4
2.3.3 The Drugs Group	5
2.3.4 The Information Group.....	5
3. Note on the Programme Against African Trypanosomiasis (PAAT)	6
4. Conclusion: Identification of future network activities	6
Annex 1: Availability and affordability of drugs.....	9
Annex 2: Priority activities of human African trypanosomiasis in WHO Department of Communicable Disease Surveillance and Response	11
Annex 3: Informal meeting on activities in anti-infective drug resistance surveillance.....	12
Annex 4: Agenda.....	13
Annex 5: List of participants.....	16

1. Introduction

Melarsoprol (Arsobal®) is the only commercial drug presently available for the treatment of advanced stage sleeping sickness cases. Melarsoprol treatment failures have been reported in the last years in Angola, the Democratic Republic of Congo, Sudan and Uganda. Some treatment centres in these countries have observed a treatment failure rate of over 20%. Reports from other centres in different countries where the disease is endemic indicate an increase in treatment failure rates sometimes more than twofold. The lack of effectiveness of existing registered drugs and the high relapse rate are of particular concern in a disease which has a CFR of 100% when untreated. However, little is known about the “incidence” of treatment failure in different geographical areas and from the scarce reports available it seems to be a growing phenomenon.

The present situation raises a number of questions which are as yet unanswered. Are treatment failures due to the intrinsic character of the parasite or are they associated with patients’ metabolism? Is drug resistance an acquired feature of the parasite when exposed to inadequate therapeutic doses? Is resistance to the drug a genetic trait of certain circulating parasite strains and can such resistant parasites be transmitted? What are the appropriate alternatives for treatment failures? What attitude should be adopted by control programmes facing non-responsiveness to drugs? Without answers to these questions, a solution cannot be found to saving the lives of patients on whom the drug has no effect. Operational and field research are needed to obtain answers. Such research can only be implemented if adequate information and biological specimens are available and the availability of information and specimens is linked to the existence of a well-structured network of collecting sites and laboratories.

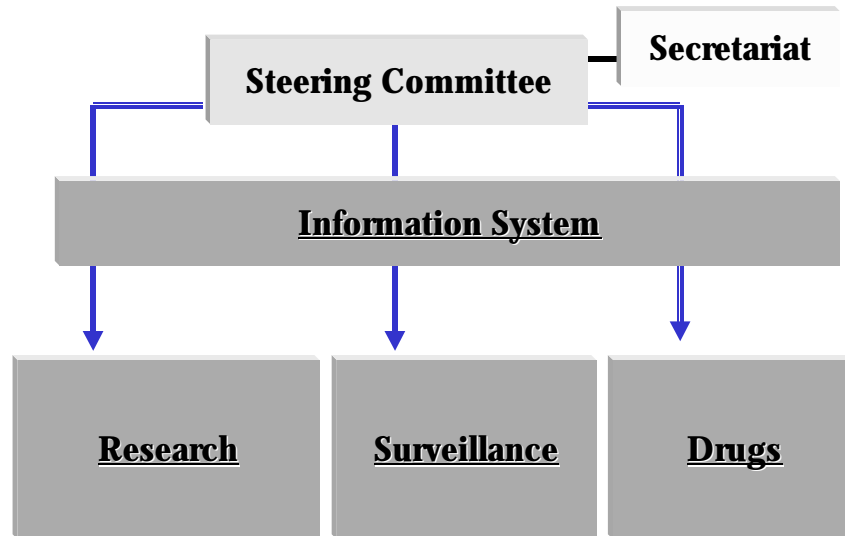
To be effective such a network needs to be coordinated to promote the necessary research and avoid duplication of work. Coordination also ensures that the required information is available and laboratories have timely access to biological specimens. In addition, such a network is expected to have a catalyzing role. The close association between field workers and scientists is expected to be one of synergy, speeding the discovery of the causes of treatment failures and relapses. The expected outcome is the rapid identification of practical solutions to the problem (Annex 1).

The establishment of a network for treatment and drug resistance falls within the mission and objectives of the Department of the Communicable Disease Surveillance and Response of WHO (Annex 2).

2. The Network

Participants approved the concept of a “Human African Trypanosomiasis Treatment and Drug Resistance Network”. The stated mission of the network was to “monitor drug resistance and find and recommend solutions for the treatment of sleeping sickness”. The defined objectives were to assess the effectiveness of current treatment regimens, collect and disseminate information on refractoriness to treatment, ensure availability and affordability of existing drugs, provide guidelines for treatment and promote research on the causes of treatment failures, drugs and treatments.

The structure of the network as defined by the participants included a Steering Committee, a secretariat and four technical working groups, each responsible respectively for research, surveillance, drugs and information. The last group would not only have its own functions but would also serve the three other groups.



2.1 The Steering Committee

The Steering Committee was defined as the driving body of the network. It would select the priorities and define the activities to be implemented. It would base its decisions on the information provided by the secretariat and individual committee members, each specializing in different subjects of interest to the network. It would establish guidelines on how to proceed to implement the mission and achieve the objectives of the network and would follow the work of the four technical groups. The Committee would meet twice a year.

2.2 The Secretariat

The secretariat would coordinate the activities of the network based on the decisions of the Steering Committee and it would be based in WHO.

2.3 The Working Groups

The working groups would coordinate the implementation of decisions made by the Steering Committee in the areas of research, surveillance, drugs and information. Each group would be placed under the responsibility of two or more Steering Committee members who would help to develop and promote the group. A plan of action would be developed by each group to be approved by the Steering Committee. It was felt that the responsibility of information collection and dissemination was best vested in the secretariat (WHO) as it served the Steering Committee as well as the other groups.

Professor P. Buscher and Dr R. Brun were requested to lead the research group. Leadership of the surveillance group was given to Dr A. Moore, Dr C. Paquet and Dr C. Burri, while Dr B. Pecoul and Dr M. Gastellu Etchegorry would head the drug group.

Steering Committee Chairman

Dr R. Brun

- 1. Research group**
Pr P. Buscher and Dr R. Brun
- 2. Surveillance group**
Dr A. Moore, Dr C. Paquet and Dr C. Burri
- 3. Drugs group**
Dr B. Pecoul and Dr M. Gastellu Etchegorry
- 4. Information group**
WHO

2.3.1 The Research Group

Resistance to trypanocidal drugs has been experimentally induced in the laboratory but drug resistant trypanosome strains have never been isolated in the field. This is probably due to the difficulties associated with parasite isolation in the field and with storage and transportation to laboratories capable of performing the appropriate studies to demonstrate resistance. The existence of intrinsically resistant parasites to melarsoprol yet remains to be demonstrated. Several hypotheses have been put forward but they need confirmation through *in vitro* and *in vivo* studies.

The threat of spread of treatment failure must be clearly assessed and adverse events during treatment and relapses must be resolved. For this the members of the Steering Committee identified the need to establish a biological specimen bank, to select a number of research laboratories to implement pertinent studies and to identify research priorities in a number of topics. The specimen bank would provide research laboratories with the essential well-documented specimens related to drug resistance and relapses. The selection of treatment centres and their constitution into a network are aimed at collecting, conditioning and storing specimens in the field. These centres, with a laboratory, would join their efforts to those of research laboratories to study the parasite and the physiological characters of patients so that the mechanisms of drug refractoriness could be identified. Various risk factors would be studied to evaluate their impact on occurrence of relapses. New protocols for existing drugs, existing drug combinations and new drugs would be considered in an attempt to develop a more effective treatment. The causes of adverse events during treatment would also be studied so as to define ways to prevent them.

It was felt that advantage should be taken of the already existing specimen banks at the Swiss Tropical Institute in Basel, Switzerland and at the Institute of Tropical Medicine in Antwerp, Belgium. These two Institutes already have a large range of well-characterized isolates and strains. They also have a large sample of biological specimens from sleeping sickness and other patients

that would be suitable for studies on resistance. Specimens to be collected within the framework of the network would then suitably complement these existing banks.

Participants decided that the role of the research group would be to:

- make an inventory of the biological material available in the existing banks;
- define the purpose for collecting and storing the future specimens;
- determine the requirements for specimens in terms of collection methods, transportation and storage;
- examine ethical issues related to specimen collection and propose methods and principles acceptable to the patient and the scientific community;
- propose criteria to define the ownership of specimen and research results;
- look at duplicate storage for important specimens;
- define rules pertaining to the use of the specimens collected;
- organize the collection of specimens through sentinel sites;
- identify and suggest research priorities in drug development, use and resistance;
- collate all possible information on ongoing research projects related to treatment and drugs.

It was proposed that a list of possible members of the research group be submitted to the Steering Committee as soon as possible. It was requested that a round table be organized to define the group's working objectives, to identify working partners, to elaborate a plan of action and to determine the target dates. The names of participants, the report and proposal would then be circulated among members of the Steering Committee for comments and approval.

2.3.2 The Surveillance Group

The major objective for the surveillance group was the establishment of a surveillance system for treatment failure and relapses. Three levels of surveillance were defined: the sentinel centres collecting treatment and relapse data in a standardized way; the centres capable of detecting trends in the occurrence of resistance and possibly collecting specimens; and the more sophisticated treatment centres which could report and analyse treatment failures and relapses as well as collect specimens. It was agreed that the surveillance group would:

- define criteria for eligibility of sentinel centres;
- propose a list of potential sentinel and treatment centres;
- define the information expected from the different centres;
- elaborate standard forms for the collection of information;
- determine different protocols for the collection of information on various subjects such as risk factors, clinical data, local use of drugs;
- organize data and specimen collection for specimen banks;
- establish an epidemiological and clinical information database closely related to the specimens collected and stored in the specimen banks.

It was proposed that a list of potential members of the surveillance group be submitted to the Steering Committee as soon as possible and that a round table be organized to define the group's working objectives and the details of the tasks to be implemented. It was also suggested that a plan of action be elaborated and target dates defined. The names of participants, the report and proposal would then be circulated among members of the Steering Committee for comments and approval.

2.3.3 The Drugs Group

Problems related to the availability and affordability of drugs require special competence. Experience with the private sector was considered essential. Thus, the members of this group had a special role to play to:

- establish links with other groups or projects dealing with availability of drugs, particularly orphan drugs;
- prepare advocacy documents and implement actions to promote partners' interest;
- establish links with industry;
- elaborate and propose an agreement with ILEX for the production of eflornithine and Ornidyl;
- propose a "common statement" agreed upon by all NGOs involved in sleeping sickness control for drug availability and payment;
- pursue discussions with the Bill Gates Foundation in support of drug availability for trypanosomiasis.

As with the two previous groups, it was proposed that a list of potential members of the drug group be submitted to the Steering Committee as soon as possible and that a round table be organized to define the group's working objectives and the tasks to be carried out. It was also proposed that a plan of action be elaborated and target dates defined. The names of participants, the report and proposal would then be circulated among members of the Steering Committee for comments and approval.

2.3.4 The Information Group

The members of the Steering Committee decided not to establish a specific group for information. They felt that the responsibility would be best vested in WHO to manage the different issues pertaining to this activity. The major objectives for the information group were defined as:

- dissemination of all information among members of the network;
- examination of the different alternatives available for wide access to the information (e. g. World Wide Web, electronic discussion lists, newsletter);
- assurance that specific information be shared with all relevant groups, including within WHO;
- elaboration and dissemination of guidelines;

- association with the PAAT¹ information system and animal trypanosomiasis network;
- close participation in the PAAT Programme.

3. Note on PAAT

The aim of the Programme Against African Trypanosomiasis (PAAT) is to “solve the trypanosomiasis problem within the broader context of food security, human health, rural development and sustainable agriculture”. PAAT has four major components: its Programme Committee, a joint FAO-WHO-IAEA-OAU/IBAR secretariat, and two modules, one on research and development and the other on policy, programme and implementation. These two modules include advisory groups on land use and environment, socioeconomic and cultural implications of trypanosomiasis, vector management, disease diagnosis and epidemiology, host management, parasite management and finally strategy and planning.

The members of the Steering Committee have agreed to request the Programme Committee of PAAT that the treatment and drug and resistance network herewith developed be included in the PAAT structure as an “advisory group”.

4. Conclusion: Identification of future network activities

The implementation of the Human African Trypanosomiasis treatment and Drug Resistance Network will include a number of practical steps:

- **the establishment of thematic working groups** – *Small groups of experts will propose activities in their particular fields of expertise. They will promote their implementation and monitor the outcome.*
- **the definition of the objectives, plans of action, targets and work schedules for each group.**
- **the preparation of guidelines for data and sample collection** - *A document will be elaborated to guide network members on how clinical data should be recorded and biological specimens collected, conditioned, stored and shipped.*
- **a meeting with selected sentinel and reference laboratories and treatment centres in charge of data and biological sample collection** - *This meeting could take place during the forthcoming International Scientific Council for Trypanosomiasis Research and Control (ISCTRC) meeting in Mombasa 27 September-3 October 1999.*
- **the elaboration of a central database and a web site to disseminate the collected information and the results of the work performed by the network.**
- **the preparation of guidelines for alternative treatments** – *Faced with patients unresponsive to the classical trypanosomiasis drug, it is urgent to*

¹ PAAT: Programme Against African Trypanosomiasis, a joint FAO-WHO-IAEA-OAU/IBAR initiative.

provide practitioners with alternative therapies. The proposed guidelines will suggest what attitude to adopt when secondary reactions occur, when patients do not respond to treatment and when relapses are observed.

- **the provision of equipment and support to reference laboratories -**
Reference laboratories will be the cornerstone of the network. They will actively contribute to the network and will be technically and financially supported to do so.
- **meetings with National Sleeping Sickness Control Programmes (NSSCPs)**
- NSSCPs will collect clinical data and biological specimens in their treatment centres. Workshops will be held during the 1999 ISCTRC meeting to explain the concept of the network and the principles on which it will function. Subsequent meetings will be held regularly to discuss and plan activities and monitor implementation. As far as possible, these meetings will be held back-to-back with other major events on sleeping sickness surveillance and control.

Annex 1: Availability and affordability of drugs

- **Pentamidine isethionate**

Pentamidine isethionate is used for the treatment of early stage human African trypanosomiasis due to *T. b. gambiense* infections. It is administered daily or every other day by intramuscular injection, 7 to 10 injections. The dose is 4 mg base per kg body weight. Most frequent adverse reactions are hypotension, abdominal pain, vertigo, hypersalivation and mild nephrotoxicity, generally reversible.

The drug is commercially available at US\$ 8 to 14 per flask from Sedapharm (France) and Schein (USA). It is also available through WHO at US\$ 3 per flask by special agreement with Rhone Poulenc Rorer. However, the agreement has recently been revised and the cost is expected to increase substantially. Rhone Poulenc has proposed a progressive cost increase to eventually reach the market price by 2004 (the current market price is FF 70, US\$ 14 per flask).

- **Suramine sodium**

Suramine sodium is used for the treatment of early stage human African trypanosomiasis due to *T. b. rhodesiense* infections. It is administered by a single weekly intramuscular injection for 6 weeks. The dose is 1 g per injection. Most frequent adverse reactions are nausea, vomiting, urticaria and less often renal damage and exfoliative dermatitis.

The drug is commercially available at US\$ 8 per flask from Bayer (Germany). On several occasions, Bayer wished to stop production but maintained it on the grounds that no other alternatives were available. Undoubtedly this issue will be raised again.

- **Melarsoprol (Arsobalâ)**

Melarsoprol is used for the treatment of the advanced stage of the disease, when the central nervous system is affected, in both *T. b. gambiense* and *T. b. rhodesiense* infections. It is administered by strict intravenous injections; 3 series of 3 injections are given with a 7 to 10 day rest period between each series. The dose is 3.6 mg per kg body weight. Several protocols have been developed in an attempt to curb adverse reactions which are myocardial damage, hypertension and exfoliative dermatitis. The most serious side effect is reactive encephalopathy which occurs in 5-10% of the patients treated with melarsoprol; 10-50% of these patients will die. Over the last 3 to 5 years an increased rate of relapses has been noticed, which is of major concern in a disease with a 100% fatality rate and in the absence of an alternative therapy.

The drug is commercially available at US\$ 8 per ampoule from Sedapharm (France). The sustained production of melarsoprol is uncertain for commercial

reasons. There are also problems associated with manufacturing the raw material required (containing arsenic) which is highly contested for ecological reasons.

Eflornithine (Ornidyl®)

Eflornithine is used in the treatment of late stage human African trypanosomiasis due *T. b. gambiense* infections. It is the only existing drug available for the treatment of patients not responding to melarsoprol. It is administered by intravenous infusion in a dose of 400 mg per kg body weight evenly divided in 4 daily infusions (every 6 hours) during 7 or 14 days. Studies have shown that the 7-day schedule is suitable in patients where melarsoprol has failed; 14 days is used in first line treatment. Adverse reactions are rather mild and reversible such as diarrhoea, anaemia, thrombocytopenia, vomiting and fever.

Today the drug is no longer available because Marion Merrell Dow stopped production when it merged with Hoechst and Roussel. WHO has not yet been able to find alternative producers for the drug. However, ILEX, a United States pharmaceutical company based in Texas, has agreed, in principle to produce the drug with a threefold increase in price (the estimated future cost of Ornidyl would then be close to US\$ 60 per bottle).

*Annex 2: Priority activities of human African trypanosomiasis in WHO
Communicable Diseases Cluster*

WHO Communicable Diseases Cluster, Department of Communicable Disease
Surveillance and Response (CDS/CSR)

Mission statement

The Department of Communicable Disease Surveillance and Response (CSR) will lead global efforts to strengthen surveillance and response for all communicable diseases which are or may emerge as public health threats.

Goals

- Strengthening epidemiological and laboratory surveillance systems using an integrated approach;
- Improving national capacity to respond to disease outbreaks and coordinating international verification and response efforts;
- Coordinating efforts to improve the surveillance and containment of drug resistant bacterial, parasitic and viral diseases;
- Coordinating efforts to improve the surveillance and control of animal and food-borne diseases as they affect human health.

Human African Trypanosomiasis (HAT) specific priorities

- Respond to specific needs as expressed by the community or by the staff responsible for HAT control;
- Ensure the sustainability of all HAT control activities;
- Collect, analyse and disseminate information. Assist all sectors involved by providing tools and expertise.

CDS/CSR objectives for HAT

- To sustain coordination of control activities to ensure continued field work;
- To enhance the epidemiological surveillance system;
- To establish a drug resistance network;
- To develop an information system;
- To collaborate with PAAT, an interagency programme.

Annex 3: Informal meeting on activities in anti-infective drug resistance surveillance

The recent internal meeting to share information about ongoing activities in anti-infective drug resistance surveillance resulted in an excellent series of disease-specific presentations which are summarised in this document. It was clear that there are many challenges in common in drug resistance activities in different diseases and that there are plenty of opportunities to share the learning experiences of individual disease programmes.

A number of areas were highlighted that might benefit from being developed by a 'horizontal', cross-cutting approach. Some suggestions are:-

- To strengthen surveillance of drug resistance through learning from the successes of various disease-specific approaches (e. g. surveillance protocols);
- To strengthen links between surveillance of resistance and surveillance of disease;
- To emphasise links between surveillance of resistance and update of treatment guidelines and essential drugs lists;
- To increase the visibility of drug resistance problems, particularly in 'orphan' diseases by linking information through a common site (e. g. Web site; publications list);
- To improve, bring together and share the information available about the range and magnitude of drug resistance and the treatment constraints that resistance imposes. Such information could include:
 - limited number of drugs available,
 - loss of drugs through resistance, leading to increasingly untreatable disease,
 - old drugs needed but no longer available,
 - new drugs needed but not accessible.
- To clarify knowledge gaps across drug resistance and research needs, and develop a research agenda (even questions as basic as vocabulary e. g. 'what is resistance/relapse/treatment failure?')
- To initiate discussions on possible WHO activities in the field of antiviral drug resistance surveillance

29 April 1999

Annex 4: Agenda

Human African Trypanosomiasis Drug Resistance Surveillance Network Meeting Geneva, Switzerland 14–15 April 1999

Opening: Lindsay Martinez, Director, WHO/CDS/CSR

Presentation of the objectives of the meeting: Jean Jannin, WHO/CDS/CSR/EDC

A committee to steer the network

It is proposed to establish a permanent “Steering Committee” to ensure the follow up of network activities and to coordinate the inputs of specific work groups.

Designation of the chairman

1. Networking

1.1 Define the network structure

1.2 Define and organize main activities

Presentation on the existing Drug Resistance Monitoring System

Rosamund Williams, WHO/CDS/CSR/DRS

Update on the drug resistance situation in Sudan

Anne Moore, CDC, Atlanta, USA

Update on the drug resistance situation in Uganda

Christophe Paquet, Epicentre, Paris, France

Update on the drug resistance situation in Angola

Christian Burri, Swiss Tropical Institute (STI), Basel, Switzerland

Update on the drug resistance situation in the Democratic Republic of Congo

Philippe Buscher, Institute of Tropical Medicine (IMT), Antwerp, Belgium

Simon Van Nieuwenhove, WHO/AFRO

2. Research

2.1 Discuss research on the causes of trypanocidal drug resistance

Update on the knowledge of resistance causes

Reto Brun, Swiss Tropical Institute, Basel, Switzerland

2.2 Maintenance of a biological sample bank at STI and/or IMT

- Agreement of STI and IMT
- Technical requirements for storage

- Technical guidelines for reference centres (sampling techniques, preservation, transport)
 - Financial aspects
- 2.3 Establishment of an epidemiological database related to biological samples**
- Case definition
 - Clinical information forms
 - Technical guidelines for reference centres
 - Data transmission
 - Financial aspects
- 3. Identification of reference centres**
- Eligibility criteria for reference centres
 - Network of research laboratories concerned with resistance mechanisms
 - Conditions for researchers to use data and samples
- 4. Collection of information on relapses**
- Network extension to include additional treatment centres
 - Basic data on occurrence of relapses and the epidemiological surveillance system
- Presentation of the “Health Data Manager/mapper” software*
Kathy O’Neill, WHO/CDS/CSR/ISR
- 5. Drug Information system**
- Information on existing drugs, new drugs, new protocols, combinations
 - Information on the ongoing studies on drug development and drug resistance
- 6. Relations with industry**
- Information on the availability of drugs.
- Update on the future of the production of existing drugs*
Pierre Cattand, WHO/CDS/CEE
- Background on the availability of eflornithine*
Felix Kuzoe, WHO/CDS/CRD
- Update on the relation with industry and donors*
Bernard Pecoul, Médecins sans Frontières, Paris, France
- Strengthen links with industry
- 7. Animal trypanosomiasis and collaboration with veterinarians**
- **Link with animal drug resistance research through the Programme Against African Trypanosomiasis (PAAT)**
 - Identification of topics of common interest to human and animal trypanosomiasis
- 8. Guidelines**
- Guidelines for appropriate treatment of relapsed cases
- 9. Establishment of a web site**
- Separate web site or inclusion into PAAT site?
 - Links with existing databases (WHO/CDS/CSR/DRS)

- Database access conditions
- Financial requirements

10. Confirmation of a Network structure

11. Plan of action for the next two years

12. Define schedule for next meetings