# HAT Platform

## Newsletter

October 2008
Issue No. 4

## EDITORIAL

**Dr Augustin Kadima Ebeja**
HAT Platform Coordinator

Thanks to the support of our partners, the regional platform for clinical trial capacity strengthening in the field of human African trypanosomiasis (HAT), more commonly known as sleeping sickness, is forging ahead.

In this fourth issue of the HAT Platform newsletter, we are pleased to share with you our experiences and to present to you the latest scientific progress made by some of our partners, particularly in the development of new diagnostics and therapeutic tools against sleeping sickness.

Since we are still in the research phase, we are aware that we still have a long way to go. But we will continue to address the most urgent needs of our region and contribute to provide adequate treatments to the most vulnerable who suffer from this disease.

In conclusion, we are looking forward to welcoming you at our next annual meeting in November during which we will update each other on the activities of the platform. At this occasion, we will be able to share our experiences and concerns with our partners, who have always given us their valuable support in the relevant training for conducting clinical trials. Through dynamic sharing of experiences, knowledge, and problem-solving techniques, we will be able to move ahead constructively!

PLATEFORME REGIONALE DE RECHERCHE CLINIQUE THA
TRYPANOSOMIASE HUMAINE AFRICAINE
HUMAN AFRICAN TRYPANOSOMIASIS
HAT REGIONAL PLATFORM FOR CLINICAL RESEARCH

We are proud to present our design for a bilingual logo that will help underscore our efforts to conduct clinical trials against this disease in the endemic countries. This logo will be officially adopted during the annual meeting of November 2008.

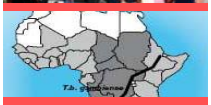
## CONTENT



P. 2 — TRAINING WORKSHOP FOR MEMBERS OF THE ETHICS COMMITTEES IN ANGOLA : A TRICONTINENTAL COLLABORATION


P. 2 — THE TRAINING OF CLINICAL MONITORS IN KAMPALA : AN ESSENTIAL MISSION

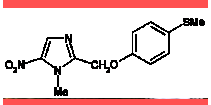

P. 3 — THE STEERING COMMITTEE MEETING IN KAMPALA


P. 3 — THE MOBILISATION OF THE AFRICAN UNION AGAINST HAT


P. 4 — DISTURBING RELAPSE RATES IN CHAD


P. 4 — A NEW ALLIANCE FOR CLINICAL RESEARCH AND EPIDEMIOLOGY IN DRC


P. 5 — A MICROSCOPE FOR THE 21ST CENTURY


P. 5 — AN UPDATE ON THE PROGRESS MADE IN THERAPEUTIC RESEARCH AGAINST HAT


P. 6 — HAT RELATED EVENTS


P. 6 — RECENT HAT PUBLICATIONS

# Training Workshop in Angola : a Tricontinental Collaboration

**Dr Vatunga Gedeão, ICCT Angola**

The HAT national control program in Angola, *Instituto de Combate e Contrôle das Tripanossomíases (ICCT)*, has organised on 14-16 May 2008 in Luanda a course for the members of ethics committees. The goal was to provide them with training on good practices in the ethical assessment of a clinical research protocol. The main objective of this course was to strengthen the capacities of the current members of the ethics committees, providing them with recent materials and procedures regarding the ethical review of biomedical research protocols. Another objective was to encourage new vocations in the field of ethical follow up and national ethics committees.

Ethic committee members in Angola, May 2008

This course was the result of a tricontinental collaboration between Africa, Europe and South America, with the HAT Platform Coordination at the core of this triangle. Thus, Angola was brought into contact with the University of Brasilia, an institution that has a solid expertise in matters of ethics committees. Our partner, Good Clinical Practice Alliance – Europe, has also contributed to the set up of the course. Like the other ethics committee trainings that were held previously by the HAT Platform in the DRC, Uganda and Sudan, this event was financed by the European Union, IncoDev, Sixth Framework Programme.

The training team was composed of four instructors (two Brazilians and two Angolans) along with the HAT Platform coordinator (Congolese). Around twenty attendees from different backgrounds were present: doctors, veterinarians, economists, lawyers, psychologists, pedagogues, nurses, laboratory personnel and civilians. At the end of the course, each participant received an attendance certificate together with a CD containing all the presentations that were made during the workshop and all the documents related to it.

According to the attendees, this training has provided access to the latest and most advanced technical and scientific learning in the field of good clinical and ethical research practices.

**Platform recommendations:**
As for the HAT Platform, the good functioning of the ethics committees depends on the help and cooperation of the local competent authorities. It is therefore highly recommended that the competent authorities accompany these recently instructed personnel.

# The Training of Clinical Monitors in Kampala : an Essential Mission

**Dr Augustin Kadima Ebeja, HAT Platform Coordinator**

Monitors working on a case study in Kampala

The training of clinical monitors has been identified as a critical aspect towards the overall strengthening of clinical trial capacities in the HAT-endemic countries.

Initially planned in Nairobi, the training had to be moved to Uganda due to the security situation following post electoral incidents that took place in Kenya earlier in 2008. The training was held at the Hotel Equatoria in Kampala from 3-6 March 2008.

Once more, the platform gave a good example of its regional diversity as it welcomed for this event the scientific team of KARI-Trypanosomiasis Research Centre (TRC) from Kenya as moderators, and could count on the platform team of the Coordinating Office for Control of Trypanosomiasis in Uganda (COCTU) for all logistic matters. Participants came from many of the HAT-endemic countries like Angola, the Democratic Republic of the Congo, the Republic of the Congo, Brazzaville, Sudan, Uganda, and Kenya.

**The following subjects were tackled during the course:**

- relationship between the ethics committee and the investigator
- role and responsibilities of the investigator
- role of the sponsor
- preliminary steps of the study
- Standard Operating Procedures
- management of adverse effects
- data management
- quality assurance and quality control

Twelve attendees benefited from this training that covered presentations, workshops and plenary sessions. Topics including a historical background on Good Clinical Practices (GCP), the international guidelines for GCP, the steps for the discovery and development of a new drug, an overview of all essential documents for a GCP study and the informed consent were discussed in detail before concentrating on the monitor's role.

As an essential part of the research team, the monitor needs to know the role and responsibilities of all other members in a clinical trial and their various interactions within the team.

We hope that we have given this first team a quite comprehensive introduction which might be followed by field trainings to be organised by the platform and under the supervision of experienced monitors.

# The Steering Committee Meeting in Kampala

**Dr Caecilia Schmid, Dr Nicolas Mbongo, Reporters, and Dr Augustin Kadima Ebeja, Coordinator**

Once more, Uganda was very generous to welcome the 6th meeting of the steering committee that was held at the Hotel Equatoria in Kampala on 9-10 June 2008. All the 21 invited members were present.

The meeting began with presentations on the achievements made by each country within the HAT Platform from December 2007 until end of May 2008, followed by an overview of what still needs to be done for 2008. Each partner proposed as well activities for the action plan 2009-2010. Furthermore, the steering committee was updated on current researches progresses.

And last but not least, a proposal for a new organisational chart for the steering committee was submitted to the attendees.

The next meeting was scheduled on November 2008 in Brazzaville during the HAT Platform annual meeting with the objective of finalising the organisational chart as well as the action plan 2009-2010.

**Topics covered:**

- Impamel III by STI (Improved application of melarsoprol in *T.b. rhodesiense*)
- Efficacy of eflornithine in Omugo, Uganda by Makerere University, Kampala
- Biological specimen bank being put together for HAT research by WHO
- Development of diagnostic tools by FIND
- Institute of Tropical Medicine Antwerp (ITMA) contribution to HAT research in the DRC.

# The mobilisation of the African Union against HAT

**Dr Joseph Ndung'u, FIND**


Participants agree on mobilising African governments to take action on human African trypanosomiasis

In January 2008, FIND has signed an agreement with the African Union Commission (AUC) in order to increase efforts to control human African trypanosomiasis (HAT) in Sub-Saharan Africa. This initiative aims to bring awareness to the HAT-endemic countries regarding this disease and to find solutions to put an end to it. It is run by the AUC coordination office of the Pan African Campaign for the Eradication of the Tsetse Fly and Trypanosomiasis (PATTEC).

PATTEC encourages all African governments' members of AU to unite in order to take action against this infectious disease and all it entails.

This collaboration will produce critical data that will be used by FIND and its partners and will allow developing a solid global access plan to diagnostics against HAT.

**With the support of FIND, PATTEC has developed a strategic plan against HAT for the next 3 years with the following objectives:**

- To synchronise all recent learning on HAT and its control
- To increase the suspicion index of HAT by health professionals
- To improve health facilities, diagnostics tools and monitoring of HAT
- To increase awareness and sense of responsibility towards HAT at local, national, regional and international levels
- To create a road map on HAT for all national policies in the endemic countries.

Representatives of the PATTEC country members, the AUO Secretary General, and the international scientific partners. Addis Ababa, January 2008

# A New Alliance for Clinical Research and Epidemiology in DRC

**Dr C Schmid et Dr C Burri, Swiss Tropical Institute, Basel, Switzerland**

ARCEAU/ DRC: Partners in a site visit. April 2008

Drugs development for the most tropical diseases has long been neglected but nevertheless important progress has been recently achieved. Although the assessment of new drugs and vaccines is a very complex endeavour, we need to increase the capacity in countries where the diseases are endemic. Even though several centres for clinical research have been opened in Africa, there are none in Central Africa nor in the Democratic Republic of the Congo (DRC).

The Swiss Tropical Institute (STI) has a wide experience in setting up international partnerships at all levels, from basic research to health structures. In the DRC for example, for 8 years on, the STI has put in place clinical studies on the human African trypanosomiasis (HAT). Thanks to donations from Bill and Melinda Gates Foundation, STI has also created a centre for clinical research in Kinshasa, DRC. Furthermore, a tripartite agreement forming the Alliance for the Clinical Research and Epidemiology in the DRC (ARCEAU/DRC), see photo above, has been signed on 21 April 2008 by the STI, the Public Health School (ESP) in Kinshasa, and the Biamba Marie Mutombo Hospital (BMMH).

Once this agreement is under implementation, all parties involved will be able to contribute to the drugs and vaccines development by taking part in the clinical studies and in doing research in the clinical epidemiology field. While the ESP in Kinshasa will concentrate its efforts mainly on malaria, tuberculosis and HIV/AIDS; BMMH will dedicate its time to doing some research on chronic diseases like high blood pressure, diabetes and cancer. In order to guarantee the continuity of research on sleeping sickness, a link will be created with the HAT national control program.

# Disturbing Relapse Rates in Chad

**Dr Francis Louis, OCEAC, Yaoundé**

In November 2006, in the endemic region of Mandoul in Chad, 145 patients who were treated 7 months earlier (April 2008) were seen for a therapeutic follow-up. Upon diagnosis, 54 of the patients were in stage 1 and 91 in stage 2, and all received treatment accordingly: 7 days of intramuscular pentamidine for stage 1 or 10 days of intravenous melarsoprol for stage 2.

Among those 154 having received pentamidine, 13 were identified as relapses at the follow-up test after 7 months, corresponding to a failure rate of 24% which is disturbingly high compared to the "usual" failure rate for pentamidine of less than 5%. Relapsed patients were subsequently treated with melarsoprol.

The OCEAC, in partnership with WHO, the University of Glasgow and the HAT National Control Program in Chad, is investigating this phenomenon in more detail.

We will need to retrieve the 13 patients who were retreated with melarsoprol in order :

- To assess the efficacy of this treatment
- To investigate possible reasons behind this high failure rate with pentamidine (could it be a bad quality of the batch, was the drug not well stored, was there an error in the dosage, or an error in the stage determination?)
- To review the evolution of the failure rate during the last 10 years and initiate research on the genetic basis of the possible resistance (mutation on the P2 transporters of purines, HAPT1 and LAPT1).

The results of these investigations will be released at the end of 2008.

# A Microscope for the 21st Century

**Dr Joseph Ndung'u, FIND**

Compared to classical microscopes, the Primo Star iLED (Light Emitting Diode) special fluorescence microscope of Zeiss (http://www.zeiss.de) is much faster with improvement in sensitivity in the detection of bacteria and some parasites; its use to visualise trypanosomes stained with orange acridine is being tested. Other specific markers to detect this parasite are also being analysed.

Recent studies have shown that the fluorescence microscope is up to 10% more sensitive than the classical microscope. FIND together with several technical partners in Uganda (NALIRRI) and the Democratic Republic of the Congo (INRB) are presently testing a commonly used fluorescent probe called the orange acridine for the detection of trypanosomes. The transmitted-light brightfield illumination requires a source of light LED of low energy that allows it to be operational continuously even during power cuts and without changing the bulb before many years. The wavelength of the light used in the fluorescent mode stimulates the most commonly used colourings bleach for the clinical detection of parasites by fluorescence. The data collected on a prototype of this microscope has demonstrated that the microscope does not necessarily require dark rooms and that it gives much clearer images than those produced by a classical fluorescent microscope, while being less expensive by far than the latter.

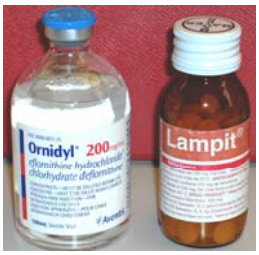
Dr Vinand Nantulya of FIND testing the new fluorescence microscope Primo Star iLED (Light Emitting Diode), developped jointly by FIND and Zeiss.

Feasibility studies are in progress in order to test the efficiency of the detection of parasites with fluorescent probes specific to trypanosomes. The goal is to develop protocols regarding the initial preparation of the sample and the colouring of the parasite with these probes. In an additional study, the most efficient probe will then be tested on the microscope with LED fluorescence.

# An Update on the Progress Made in Therapeutic Research against HAT

## NECT Dr Els Torreele, DNDi

The NECT study aims to test the safety and efficacy of a simplified combination of nifurtimox with eflornithine (N+E Combination Therapy) treatment for stage 2 HAT compared with the standard treatment of 14 days eflornithine monotherapy.



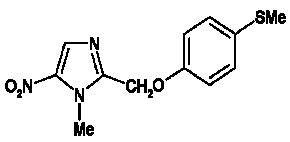

The enrolment of patients in the Democratic Republic of the Congo (DRC) and the Republic of the Congo (RDC) ended late 2006, and the 18-months follow-up of patients to establish efficacy could be completed in July 2008. Overall, the four sites in the DRC and the RoC have recruited a total of 287.
The safety analysis showed that both treatments are well tolerated, especially in comparison to melarsoprol (much less toxic) even though some differences were noticed in their safety profile. The efficacy analysis will be available in the near future.

The next steps for **NECT** are:

- The final report of the NECT study (on safety and efficacy)
- Submitting an application to add nifurtimox, to be used in combination with eflornithine, on the WHO List of Essential Medicines (EML) for stage 2 HAT.
- Set up a pragmatic study, NECT-FIELD, with the objective to further document the safety and feasibility of the combination in "real life" conditions. This study will be initiated in DRC, but could be extended to other countries during 2009.

## Fexinidazole Dr Els Torreele, DNDi

Fexinidazole is a new drug candidate being evaluated and developed by DNDi. It belongs to the nitroimidazole family, and can be given by the oral route. It crosses the blood-brain barrier and is effective in animal models of stage 1 and 2 HAT in vitro, it was also shown active against both the rhodesiense and gambiense trypanosomes species.




The preclinical development of fexinidazole is currently being completed with the objective of starting phase I First-in-Human studies early 2009.

## DB289 Dr Cecile Schmid, STI

The development of a promising compound known as DB289 (maleate of pafuramidine) has been stopped abruptly on 26 December 2007 by the FDA. In a press release issued on 22 February 2008, Immtech reportedly announced that the project was halted due to new data collected on the safety of its use.

The next steps for **DB289** are:

- A comprehensive follow-up during a 24 months period of HAT patients in the DRC (approximately 45%)
- An in-depth biochemical assessment in Vanga, Kikongo and Bandundu
- The final report of the study.

## HAT Related Events

**The 17th International Congress on Tropical Diseases and Malaria was held in Jeju, South Corea, in early October 2008.** Two sessions on HAT were on the agenda which included presentations on the HAT Platform (Dr A Ebeja), the final results from the NECT study (Dr G Priotto), and the strategy adopted by DNDi for the discovery of new drugs for HAT (Dr E Torreele).

**The 4th HAT Platform annual meeting will be held in Brazzaville, 18-19 November 2008** together with the steering committee meeting.

**The 57th Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) will be held in New Orleans, USA on 7-11 December 2008.** Drs Pere Simarro and Leon Kazuma will co-chair a DNDi-organised HAT treatment R&D session, with planned presentations on the HAT Platform (Dr F Kansiime), NECT study results including additional efficacy analyses (Dr G Priotto), an update on HAT-related research results of the diamidine family (Dr C Olson), and an update on fexinidazole, which will be moved into clinical development next year (Dr E orreele). DNDi will also co-sponsor together with sanofi-aventis a separate symposium on malaria.

Project Coordinator : Dr Augustin Kadima Ebeja
Editorial Committee: Drs V. Gedeão, J. Ndung'u, F. Louis, C. Schmid, E. Torreele, Nicolas Mbongo, C. Burri.
Editor: S. Kaenzig, DNDi
Translator/ Reviser: Z. Jallad
Design and layout : M. Lucas Subirats, DNDi

## Recent HAT Publications

Checchi, F., Barrett, M. P.; African Sleeping Sickness. BMJ 2008, 336 (7646), 679-680

Checchi, F., Filipe, J. A., Haydon, D. T., Chandramohan, D., Chappuis, F.; Estimates of the duration of the early and late stage of gambiense sleeping sickness. BMC Infect Dis 2008, 8, 16.

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Dorlo, T. P., Kager, P. A.; Pentamidine dosage: a base/salt confusion. PLoS Negl Trop Dis 2008, 2 (5), e225

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Njiru, Z. K., Mikosza, A. S., Matovu, E., Enyaru, J. C., Ouma, J. O., Kibona, S. N., Thompson, R. C., Ndung'u, J. M.; African trypanosomiasis: sensitive and rapid detection of the sub-genus Trypanozoon by loop-mediated isothermal amplification (LAMP) of parasite DNA. Int J Parasitol 2008, 38 (5), 589-599.

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Simarro, P.P., Jannin, J., Cattand, P.; Eliminating human African trypanosomiasis: where do we stand and what comes next. PLoS Med 2008, 5(2), e55

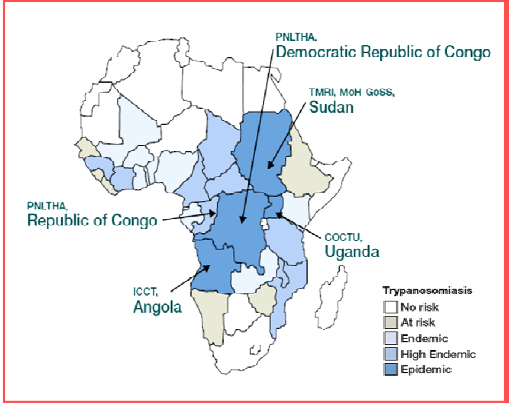
Robays, J., Nyamowala, G., Sese, C., Betu Ku Mesu Kande, V., Lutumba, P., Van der Veken, W., Boelaert, M.; High failure rates of melarsoprol for sleeping sickness, Democratic Republic of Congo. Emerg Infect Dis 2008, 14 (6), 966-967

Robays, J., Raguenaud, M. E., Josenando, T., Boelaert, M., Eflornithine is a cost-effective alternative to melarsoprol for the treatment of second-stage human West African trypanosomiasis in Caxito, Angola. Trop Med Int Health 2008, 13 (2), 265-271.

Steverding, D.; The History of African Trypanosomiasis. Parasite Vectors 2008, 1 (1), 3.

## HAT Platform Mission

The HAT Platform is a scientific and technical regional network dedicated to the human African trypanosomiasis (HAT), more commonly known as sleeping sickness. Its main objective is to set up a pool of highly qualified regional skills through relevant training in order to facilitate clinical trials and develop new diagnostics and treatment tools against the disease.




Founded in 2005, this network, available to all, is composed of members from the HAT national control programmes of the endemic countries such as the Democratic Republic of the Congo, the Republic of the Congo, Angola, Uganda, and Sudan in partnership with STI, DNDi, WHO, FIND, ITMA, and KARI-TRC.

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