HAT Plateform

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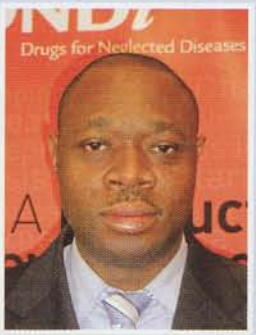
PLATEFORME REGIONALE DE RECHERCHE CLINIQUE THA
TRYPANOSOMIASE HUMAINE AFRICAINE
HUMAN AFRICAN TRYPANOSOMIASIS
HAT REGIONAL PLATFORM FOR CLINICAL RESEARCH

editorial



Augustin Kadima Ebeja (Coordinator of the HAT platform)

It is not easy to communicate correctly through a newsletter, but our platform has accepted this challenge for the fifth time. This time however, a new editorial committee has been set up with the following members: Gédéon Vatunga from Angola; Stéphane Ngampo from Congo Brazzaville; Pascal Lutumba from IMT.Antwerp, Els Torreele from DNDi Geneva, Intisar Elrahay from the Sudan, Cecile Schmid from STI Basel, Sadia Kaenzig from DNDi Geneva, and the platform coordinator Augustin Kadima Ebeja.

Our aim is to produce a newsletter which is meaningful and remains up to date for as long as possible. The editorial committee is responsible for proposing topics, organising the submission of relevant articles, and finally selecting and harmonising the articles to be published. For article review and newsletter design, we rely on the specialists of the DNDi communications team (Z. Jallad and M. Lucas).

We have good news to report: NECT has been added to the WHO Essential Medicines List at the end of April 2009. This means that national control programmes can now have access to the new treatment by making requests to the Neglected Tropical Disease Control Program of the World Health Organization, who, with the help of MSF-Logistique, coordinates treatment kit preparation and delivery to national capitals.

The success of NECT is due to the combined efforts of many partners, including the HAT Platform.
In the current issue, we focus on this important moment (and the clinical trial success which served as as the core for the Essential Medicines List application) along with a summary of our platform's annual meeting. We also present information on the meeting's main topics (i.e. the diagnosis, treatment, and follow-up of HAT); along with upcoming meetings related to HAT.

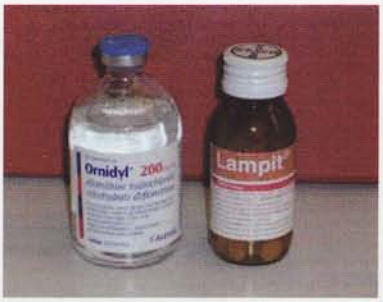
Finally, we would like to thank all those who were involved in bringing this issue to life, and we express our gratitude to all the platform members: without you, the newsletter would not exist. See you soon for the sixth edition.

Sommaire

2. NECT : 1st improved treatment in 25 years now ready to be used as NECT added to the WHO Essential Medicines List

Els Torreele

As reported during the HAT Platform meeting in Brazzaville, pivotal Phase III clinical trial results conclusively show that Nifurtimox-Eflornithine Combination Therapy (NECT) is well tolerated and effective against the advanced stage of T. b. gambiense sleeping sickness, a fatal disease that threatens 60 million people in sub-Saharan Africa



According to the WHO, NECT can now be used in patients and will provide an opportunity to improve the management of sleeping sickness cases. WHO has already made preparations for the arrival of this improved therapeutic opportunity and will work to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

NECT, the co-administration of oral nifurtimox and intravenous eflornithine, is made available through donations to WHO by sanofi-aventis for eflornithine and Bayer for nifurtimox. The pivotal, 5-year long Phase III study comparing NECT with eflornithine used alone was recently completed by a partnership including Epicentre, Médecins Sans Frontières (MSF/Doctors Without Borders), DNDi, the Swiss Tropical Institute (STI), and the national sleeping sickness control programmes of the Republic of the Congo (RoC) and the Democratic Republic of the Congo (DRC).

Epicentre and MSF initiated the study in 2003 at Nkayi, RoC, along with the national HAT control program. The trial, which was conducted according to international Good Clinical Research Practice (GCP) standards, was extended to additional sites in DRC by Drugs for Neglected Diseases initiative (DNDi) in 2004: Epicentre, MSF, the Swiss Tropical Institute (STI) and the national HAT control program contributed to the study's conduct in the DRC. The convincing final results served as the core of the successful EML application and will soon be published in the Lancet.

The clinical trial enrolled 280 patients and was completed in five years. It compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 T. b. gambiense sleeping sickness. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

As was presented during the meeting my members of the team at the Dipumba Hospital in DRC, the personal commitment made by the field team – including site investigators, nurses, laboratory workers and other health staff – was instrumental to the success of conducting and completing a quality study held to international standards in the remote and resource-limited conditions.

With some of the strongest clinical research evidence to date, the trial conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine monotherapy. As presented by trial's principal investigator, Dr. Gerardo Priotto of Epicentre during the meeting, NECT is a far more practical treatment than eflornithine monotherapy (which requires 56 round-the-clock injections over 14 days) because the number of injections is reduced to 14, the frequency of injections is halved, and the treatment duration is reduced to 10 days. This schedule better fits the routine of health

NECT In A Nutshell

Compared to eflornithine monotherapy as shown in the Phase III study, NECT was shown to be:

- Non-inferior in terms of efficacy: 97% to 98% for NECT (depending on analysis approach)
- Well-tolerated, with low fatality rates in both arms
  - Diarrhea, fever, infection, anorexia, and hypertension more frequent with eflornithine treatment
  - Nausea and/or vomiting more frequent with NECT
- The number of infusions of eflornithine is reduced from 56 to 14:
  - Less burdensome for the health care staff
  - Less risk of infections
  - More convenient for the patient
- The treatment duration is reduced from 14 to 10 days:
  - Less expensive for the severely cost-constrained health system
  - More capacity for the treatment centre
  - More convenient for the patient
- The number of infusions per day is reduced from 4 (every 6 hours) to 2 (every 12 hours):
  - Less burdensome for the health care staff: no need for nighttime care
  - More convenient for the patient
- Reduced logistical challenges:
  - Smaller volume/weight (cheaper transportation)
  - A treatment kit can contain 4 instead of 2 full treatments in a ~35 kg package
- Resistance is less likely to develop as the two drugs have different modes of action, thus mutual protection is to be expected.

care centers because infusions are reduced to twice a day, without nighttime infusions.

"NECT provides patients with a new and improved treatment of stage 2 sleeping sickness, and should reduce the use of melarsoprol, a toxic drug which kills 1 in 20 patients," remarked Bernard Pécoul, Executive Director of DNDi. "However, it is still a far-from-ideal treatment because it requires infusions and trained health care staff; DNDi remains committed to further research efforts into delivering innovation that will best meet the needs of the most neglected patients."

"The results of the NECT study instill hope in practitioners and patients across sub-Saharan Africa," remarked Dr. Constantin Miaka Bilenge, the Special Advisor to the HAT National Control Program of the DRC. "We are looking for an easy-to-use treatment that can improve case management in the field, and NECT provides us this practical improvement."

3. Highlights of the 2008 HATCap Annual Meeting - Brazzaville (Congo)

N. Mbongo, S. Ngampo, and H.J. Parra

The annual meeting of the HAT Clinical Trial Capacity Building and Strengthening Platform (HATCap) was held in Brazzaville, Congo, on November 18 and 19, 2008, in Hotel Laîco, Maya Maya.

It was attended by the members of the Platform, as well as physicians, pharmacists, academic researchers and NGO partners involved in the control of sleeping sickness.

Three years after launching the HAT Platform, this meeting's main objective was to exchange information on the capacity building and strengthening activities of each member country, and on the progress made in research to improve the management of sleeping sickness.

Over 50 participants from Angola, the Sudan, DR Congo, Switzerland, Belgium, France, Italy and the Republic of the Congo took part in the meeting.

The opening address was given by the General Director of Health of the Republic of the Congo, Dr Damase BODZONGO, the General Director of Health and Special Adviser to the President of the Republic of the Congo, Pr. H J PARRA, and the Executive Director of DNDi, Dr Bernard Pécoul. The meeting was divided into four sessions:

- HAT Platform and HAT epidemiology,
- New treatment for stage 2 HAT (NECT: Nifurtimox-Eflornithine combination),
- On-going research & development, and
- Capacity building and strengthening and partnerships.

After two days of fruitful exchanges, the conclusions were:

- The HAT Platform continues to grow as a useful venue to share research progress and harmonize a regional approach
- Much work remains to be done to deliver the ideal new treatment (effective, well tolerated, easy to use, and preferably active on both stages of the disease), but major progress has been seen with the promising results of the NECT study
- NECT is very promising and therefore endemic countries must push for this drug to be added onto their essential medicines list
- Training schemes for the staff involved in clinical trials have been carried out with the support of partners such as the European Union, but they need to be extended.

With the exception of the clinical trial on DB289, which should be terminated for good in March 2009 (inconclusive for reasons explained during the meeting), the other ongoing and planned studies are progressing as planned:

- THARSAT: shortening post-treatment follow-up
- NECT-FIELD: evaluating the tolerability, feasibility, and effectiveness of NECT in "real-life" conditions and in special populations like children; study will begin patient enrolment in DRC in the 1st half of 2009
- Markers of treatment efficacy: current situation and how can we do better?
- Progress and prospects in new diagnostic tools
- Towards « staging » and accurate follow-up of human African trypanosomiasis
- Fexinidazole: first-in-human, Phase I studies will begin with healthy normal volunteers in 2009

o Fexinidazole is seen as huge hope for sleeping sickness as it's been shown, in animal models, to be active against both Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense, to be able to cross the blood-brain barrier, and to be orally bioavailable.

For publications and/or details on these topics, contact the Platform coordination.

The Platform is emerging as a real multidisciplinary structure focusing on information exchanges and training of the actors involved in the control of sleeping sickness at a sub-regional level.

The closing ceremony was chaired by Dr Damase BODZONGO who pointed out that, after the OCEAC meeting in September and the PATTEC meeting in October 2008 in Brazzaville, this meeting also helped to increase national and international awareness on the health issue posed by sleeping sickness, and on the dire necessity to rally yet more support for the control of this neglected disease.

The General Director of Health of Congo-Brazzaville ended his address by congratulating the participants, stressing the importance of the conclusions of this Brazzaville meeting and the necessity to include them in the action plan for 2009-2010.

4. Institut Pasteur in Brazzaville and LNSP: fighting sleeping sickness together

Nicolas Mbongo, Stéphane Ngampo** and HJ Parra**

The Institut Pasteur in Brazzaville was founded in 1908 by the authorities of French Equatorial Africa (AEF), which included Congo-

Brazzaville, Gabon, Central African Republic and Chad, and by the Institut Pasteur in Paris. The institute was founded by AEF after a research mission led by Martin, , Leboeuf and Roubaud, where they found that sleeping sickness was devastating French Congo and a large part of colonial Africa at the time (1906-1908).

Laboratoire National de Santé Publique
Cité Louis Pasteur, Brazzaville, République du Congo

This mission provided valuable scientific insight into the epidemiology of sleeping sickness, as associated with population movement (railway construction, trading, administration...); the role of insect vectors (tsetse flies) in the disease; the necessity for systematic screening and early detection of the disease to improve the efficacy of treatments (atoxyl, arsenic trisulfide, lomidine); and the description of foci.

In Congo-Brazzaville, the disease is still prevalent in the same locations as those of the historical foci: Bouenza foci between Brazzaville and Pointe-Noire, Ngabe-Mpouya foci on the river Congo, and Loukolela-Mossaka foci.

At the end of the colonial period (1960), the prevalence of the disease had dropped. However, less than a decade later, new outbreaks were seen, with a prevalence near 10% (Bouenza foci), and up to 20% (Ngabe-Mpouya foci).

In 1969, LNSP (Laboratoire National de Santé Publique) was created to replace the Institut Pasteur of Brazzaville. It still works on sleeping sickness with the Service des Grandes Endémies and the Office de Recherches Scientifiques des Territoires d'Outre Mère (ORSTOM) (current IRD). Since the closure of ORSTOM following the creation of PNLTHA (Programme National de Lutte contre la Trypanosomiase Humaine Africaine) in 1985, the activities of Institut Pasteur Brazzaville have focused mainly on epidemiological surveillance.

Since the armed conflicts from 1993 to 1998, the HAT situation has worsened. Between 1998 and 2000, almost 80% of the patients were identified at the advanced, neurological stage of the disease. In 2002, with the support of World Health Organization (WHO) /Tropical Diseases Research (TDR) and OCEAC (Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale), LNSP launched a new research program on HAT, with three well-defined objectives: (1) discovery of new potential drugs based on medicinal plants, (2) implementation of clinical trials, and (3) training of personnel.

Other collaborative projects were set up with international institutions, such as the Kenya Agriculture Research Institute – Trypanosomiasis Research Centre (KARI-TRC), the University of Cambridge, the University of Bristol, the London School of Hygiene and Tropical Medicine (LSHTM), the Swiss Tropical Institute (STI), and the University of Makerere. These projects include:

i) Study and mapping of trypanosome chemosensitivity and markers of drug resistance, 2002-;
ii) Follow-up of CATT-positive individuals apparently without parasitemia compared to CATT-negative individuals without parasitemia living in T.b. gambiense-endemic foci in the Republic of the Congo and Cameroon, 2004-;
iii) HAT staging, 2005-; 2004-;
iv) HAT clinical trial capacity building and strengthening platform (HATCap), 2005-;
v) HAT control strategy at sub-regional level – Central Africa, 2006-;
vi) Development and implementation of HAT monitoring tools for national programs based on tsetse flies, 2008

All these projects are benefitting from new international initiatives on sleeping sickness (WHO/Sanofi-Aventis, PAAT, PATTEC, DNDi) and from the support of public authorities, with the organisation of the 1st International Congress in Brazzaville on Tsetse Flies and Trypanosomiasis (23-25 March, 2004).

5. Pharmacovigilance at the PNLTHA (National HAT Control Program)

Jacquies Makabuza1, Pascal Lutumba 1,2
1Programme National de Lutte contre la THA (PNLTHA) in DRC, 2ITMA, Belgium

Cases of melarsoprol failure have been reported since the 1990s. The true proportion of these failures is unknown and a matter of controversy. This lack of precise data has lead to poor management of the failure cases, as a large number of these patients were re-treated several times with melarsoprol. Towards 2005, i.e. over ten years later, a consensus has appeared on the reality of melarsoprol failure, with over 50% of cases occurring in the province of East Kasai (personal communication, Anne Moore). To help monitor the efficacy of HAT treatments and any toxicity issue, PNLTHA/DRC, with the support of IMT Antwerp, set up a surveillance system to allow for early detection of any adverse events and trypanocidal failure.

This system is based on the current system of surveillance and data collection. However, a few improvements were necessary, such as introducing a unique code for each patient, changing the information circuit, creating a side effect datasheet, and making data collection and processing electronic.

In 2009 and 2010, a pilot study will be conducted in three regions in DRC: North Bandundu, South Bandundu and East Kasai. The lessons learned during this pilot stage will help to adapt the tools (if necessary) and extend their use throughout the country, should to the early results be successful.

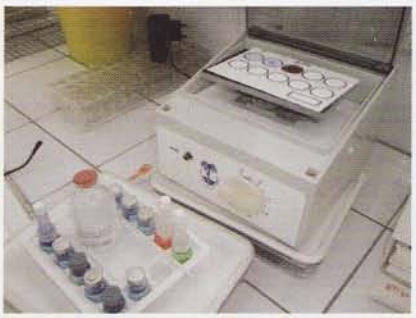
The new datasheets have been distributed in the field, and data collected in these three areas from 2006 to 2008 are currently

being entered in the computer. The first analysis of the system is expected in the first quarter 2010.

The advantage of this system is that it will provide efficacy and toxicity indicators for the products used in the program, and it will also reduce the administrative workload of the mobile units, the coordination and the central administration.

6. CATT-D10 for the diagnosis of human African trypanosomiasis (HAT)

Patrick Mitashi
University of Kinshasa, Department of Tropical Medicine, Service of Parasitology
Democratic Republic of Congo



HAT screening tests are used to detect subjects within the population suspected of having sleeping sickness. This is a simple serological test: CATT (Card Agglutination Test for Trypanosomiasis). Up until now, this test was provided by IMTA (Institute of Tropical Medicine - Antwerp) in a kit of 50 doses specially designed for mobile units. This screening test requires cold storage. Its use in permanent facilities raises the following problems: loss of reagent, poor conservation. Especially for permanent facilities, IMTA has developed another type of CATT (D10) which is more stable and also cheaper. Its validity had to be tested in the field after good results were confirmed under laboratory conditions in Antwerp.

The field results obtained with CATT whole blood showed a good match between old and new formats. In the IMTA laboratory, the CATT dilution used on both CATT formats also showed a good match. Likewise, the results of thermal stability of CATT D10 were also very satisfactory.
Therefore, this reagent may enable permanent health facilities in their HAT screening role.. The results will be presented during the next Platform meeting (June, Nairobi) and published shortly.

7. Recent scientific events and miscellaneous information

7.1) Participation of the Platform members at the 57th annual meeting of ASTMH (American Society of Tropical Medicine and Hygiene).

During the most recent meeting of the American Society of Tropical Medicine and Hygiene on December 8th, 2008, in New Orleans, DNDi organised a symposium called « Addressing research and development challenges by providing new drugs for human African trypanosomiasis: potentials in the pipeline and recent clinical trials » co-chaired by Pere Simarro of WHO/NTD and Leon Kazumba, HAT Platform member.

Some members of our platform also contributed to the following presentations:

- Current successes of the HAT Platform, challenges and opportunities to solve the difficulties inherent to clinical research on HAT drugs and to the development of a regional research platform
  - o By Fred Kansiime, HAT Platform, Coordination Office for Control of Trypanosomiasis in Uganda (COCTU), Kampala, Uganda
- Results of a phase III multicentre study evaluating the NECT combination for the treatment of stage 2 HAT.
  - o By Gérarodo Priotto, Epicentre, Paris, France
- Results of the study evaluating the diamidine class for the treatment of HAT
  - o By Carol Olson, Immetech pharmaceuticals, Vernon Hills, IL, USA
- Fexinidazole: rediscovery of nitroimidazole as a drug candidate, under clinical development for HAT treatment
  - o By Els Torreele, Drugs for Neglected Diseases Initiative (DNDi), Geneva, Suisse.

NECT Press Releasing

Other contributions were made by members of the HAT Platform: Constantin Miaka Mia Bilenge representing ARCEAU-RDC and Christian Burri for STI who discussed the challenges of clinical trials on HAT.

7.2) Support from the HAT Platform to add NECT on the WHO Essential Medicines List

Given the positive results demonstrated in the NECT study, DNDi submitted an application requesting that the WHO add NECT onto its list of essential medicines, so that countries can then be advised to use this combination to treat patients with second stage T.b. gambiense trypanosomiasis.

Several members of the HAT community, including CDC, MSF, STI,

EANNETT, and KARI-TRC, have provided support statements for DNDi's application.

DRC, being the most affected country in the world and having experienced the advantages of this treatment during the study carried out in three sites in its territory, also supported this application. Representatives of PNLTHA, INRB, and a provincial parliamentarian joined the HAT Platform coordinator in signing this document (available on the WHO website).

7.3) Participation of the Platform members to the PATTEC meeting

From January 19 to 20, 2009, a workshop was organised in Addis Ababa, Ethiopia, to finalise the PATTEC program's action plans on the advocacy and implementation activities for the control and elimination of tsetse flies and trypanosomiasis.

With the support of FIND, representatives of all five countries members of the HAT Platform (Angola, DRC, Republic of the Congo, Uganda and the Sudan), and the Platform coordinator joined the fifty or so participants from several endemic countries (Central African Republic, Ivory Coast, Gabon, Guinea Conakry, Kenya, Malawi, Nigeria, and Tanzania) who attended this meeting, along with various scientific and political partners of the programme.

PATTEC meeting Participants en Adis Ababa

Each country presented its advocacy plan, which is aimed at increasing both awareness and resources for the control of this neglected disease.

Research being one of the most important means to achieve the ultimate objective of PATTEC (control and elimination of tsetse flies and trypanosomiasis), our platform along with other scientific partners called for collaboration which would use the competencies of each partner to achieve the objectives that heads of African states assigned to PATTEC.

8. Upcoming meetings

1) June 23-24: 2nd Annual Meeting of DNDi and the 3rd Meeting of DNDi Africa,, Nairobi, Kenya.
2) June 25: HAT Platform Steering Committee meeting, Nairobi, Kenya
3) September 6-10: 6th European Congress of Tropical Medicine and International Health (ECTMIH), Verona, Italy.
4) September 21-25: 39th International Scientifc Congress on Research and Trypanosomiasis (CISRCT), Entebbe, Uganda,
* The Annual Meeting of the HAT Platform jointly with EANNET and 2nd Steering Committee Meeting.
5) November 4-6: 5th International Congress of Infectious and Parasitic Diseases (CPIP) Kinshasa, Democratic Republic of Congo.

9. Recent publications on HAT

1) Balasegaram, M., H. Young, et al. (2009). «Effectiveness of melarsoprol and eflornithine as first-line regimens for gambiense sleeping sickness in nine Médecins Sans Frontières programmes.» Trans R Soc Trop Med Hyg 103(3): 280-90.
2) Blum, J. A., C. Schmid, et al. (2009). «Cardiac Alterations in Human African Trypanosomiasis (T.b. gambiense) with Respect to the Disease Stage and Antiparasitic Treatment.» PLoS Negl Trop Dis 3(2): e383.
3) Cecchi, G., M. Paone, et al. (2009). «Towards the Atlas of human African trypanosomiasis.» Int J Health Geogr 8: 15.
4) Checchi, F., J. A. Filipe, et al. (2008). «The natural progression of gambiense sleeping sickness: what is the evidence?» PLoS Negl Trop Dis 2(12): e303.
5) Fevre, E. M., B.V. Wissmann, et al. (2008). «The burden of human african trypanosomiasis.» PLoS Negl Trop Dis 2(12): e333.
6) Kennedy, P. G. (2008). «The continuing problem of human African trypanosomiasis (sleeping sickness).» Ann Neurol 64(2): 116-26.
7) Kennedy, P. G. (2009). «Cytokines in central nervous system trypanosomiasis: cause, effect or both?» Trans R Soc Trop Med Hyg 103(3): 213-4.
8) Mumba Ngoyi, D., V. Lejon, et al. (2009). «Comparison of operational criteria for treatment outcome in gambiense human African trypanosomiasis.» Trop Med Int Health 14(4): 438-44.
9) Rodgers, J. (2009). «Human African trypanosomiasis, chemotherapy and CNS disease.» J Neuroimmunol.
10) Kandolo Tshimungu, Barthélemy Banza et al (2008) "Knowledge, behaviours, practices and beliefs regarding Human African Trypanosomiasis (HAT) among inhabitants of Kinshasa (Democratic Republic of Congo)" Cahier Santé 18 (3)