HAT Platform

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SPECIAL ISSUE

Annual Scientific Meeting 2010

Silver Springs Hotel, 6th October 2010, Nairobi, Kenya

DNDi Drugs for Neglected Diseases *initiative*

FIND foundation for innovative new diagnostics

EANETT

Summary

Éditorial

This eighth issue focuses on the highlights of the joint EANETT-HAT PLATFORM annual scientific meeting. The Platform coordination takes this opportunity to wish all our readers and partners happiness and success in 2011. You will also find our regular articles on the latest scientific events, upcoming meetings in 2011, and recent publications on HAT.

With our very best wishes.

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JOINT HAT PLATFORM – EANETT ANNUAL SCIENTIFIC MEETING

a) Joint Communiqué from the Eastern Africa Network for Trypanosomiasis (EANETT) and the HAT Platform, Silver Springs Hotel, 6th October 2010, Nairobi, Kenya

The Eastern Africa Network for Trypanosomiasis (EANETT) and the Human African Trypanosomiasis Platform (HAT Platform) held a joint Annual Conference at the Silver Springs Hotel, Nairobi, on the 4th and 5th of October 2010. The event was supported by DNDi (Drugs for Neglected Diseases initiative) and FIND (Foundation for Innovative New Diagnostics). The conference was officially opened by Dr. Ephraim Mukisira, Director, KARI, and attended by researchers and disease control experts from sixteen countries, eight of which are endemic for sleeping sickness. International collaborators and other organizations involved in research and control of HAT also participated.

This conference, the first held jointly by EANETT and the HAT Platform, covered on-going research in tsetse and trypanosomiasis in member countries, and efforts being made to control the disease. The broad areas that were covered included country reports, target product profiles, HAT treatment and clinical trials, drug discovery and animal models diagnostics, epidemiology, entomology, public health and socio-economics. Participants applauded the success of the event and recommended that both EANETT and the HAT Platform should ensure that similar conferences be held in the future. The data and information generated and shared under the joint activities will facilitate development of innovative strategies for HAT control/elimination.

From the foregoing, and considering that the forum created a unique opportunity for researchers and implementers to share information, both EANETT and the HAT Platform pledge to go ahead with, and sustain, this initiative in an integrated and multidisciplinary manner in support of ongoing efforts towards elimination of African trypanosomiasis. This will lead to improved livelihoods for the rural impoverished communities in sub-Saharan Africa.

Dr Grace Murilla
Chairperson, EANETT

Dr Augustin K. Ebeja
Coordinator, HAT Platform

b) Sessions reports

The conference opened with a welcome address by Dr. Grace Murilla, followed by a brief prayer by Dr. Augustin Ebeja, and the presentation of the participants. The sessions were attended by approximately 100 people representing 16 countries.

Dr. Augustin Ebeja and Dr. Grace Murilla introduced their organisations, i.e. the HAT Platform and EANETT, respectively.

The HAT Platform is a network whose main aim is to bring together researchers and control programs from the countries affected by human African trypanosomiasis. Its objectives are to harmonise research tools, knowledge and training, as well as promote the implementation of results produced by the various studies. At the time of its creation in 2005, the HAT Platform included five member countries: DRC, Republic of Congo, Uganda, Sudan, and Angola. Two new members have since joined: Chad and the Central African Republic (CAR).

EANETT was created in 2000 with the help of STI. It included seven countries: Kenya, Tanzania, Zambia, Malawi, Uganda, Sudan, and Switzerland. DRC has since joined as a new member. The aim of EANETT is to promote research contributing to an effective management of sleeping sickness.

Session 1 - Country reports

Chairman: Atway Msangi; Reporter: Dieudonné Mumba Ngoyi. The session included 14 presentations.

The number of HAT cases has dropped in every country, with the exception of CAR. Major efforts were undertaken

Participants at the joint HAT PLATFORM–EANETT annual scientific meeting, Nairobie, october 2010

SCIENTIFICS PRESENTATIONS SYNOPTIC TABLE

N°	TITLE OF THE PRESENTATION (SUBJECT)	SPEAKER	INSTITUTION
	SESSION 1 : COUNTRIES REPORTS		
1	**TANZANIE:** Tsetse and Trypanosomiasis Research and Capacity Building activities, 2008-2010	Mramba	TTRI
2	**MALAWI:** The epidemiology of trypanosomiasis in Rumphi District, Malawi: A ten year retrospective study	Madanista	University of Malawi
3	**ZAMBIA:** Tsetse and Trypanosomiasis Research activities in Zambia	Sinyangwe	CVRL
4	**KENYA:** Tsetse and Trypanosomiasis Research and Capacity Building activities, 2008-2010	Grace Murilla	TRC
5	**UGANDA:** Current HAT situation and possibility of convergence of two forms of HAT in Uganda	Enock Matovu	Makerere University
6	Epidemiology (table with data from all HAT Platform countries)	Victor Kande Betu Kumeso	PNLTHA RDC
7	Diagnostic tools or on going trials in all HAT Platform countries	Gedeão Vatunga	ICCT Angola
8	Current research capacity in HAT Platform countries	Nicolas Mbongo	LNSP Congo Brazzaville
9	Challenges and way forward in all HAT Platform countries	Richard Laku	MoH GoSS Sudan
10	Relatively quick reduction of caseload in a remote HAT focus through active and passive screening in CRA	Kai Braker	MSF-Amsterdam
	SESSION 2: PROFIL DU MÉDICAMENT IDÉAL		
11	Presentation and open debate– Target Product Profile (TPP)	Olaf Valverde	DNDi Geneva
	Session 3 : TREATMENT/CLINICAL TRIALS		
12	Nifurtimox- Eflornithine Combination Treatment (NECT) extension	Pere Simarro	OMS
13	Nifurtimox-Eflornithine Combination Treatment condition de terrain (NECT-Field)	Cecile Schmid	Swiss TPH
14	Tolerance and feasibility of Nifurtimox-Eflornithine Combination Therapy (NECT) for second stage T. b. gambiense HAT in Doruma, north-east DRC	David Schrumpf	MSF Geneva
15	Fexinidazole: Update on Phase I Clinical Trial.	Nathalie StrubWourgaft	DNDI-Geneva
16	Necessity of developing pharmacovigilance activities for trypanocidal drug in affected areas.	Michel Ntama	UNIKIN DRC
	SESSION 4 : DRUG DISCOVERY/ANIMAL MODELS		
17	Identification and modes of action of new anti-trypanosome molecules	Mariette Dethoua	Institut Pasteur, Bangui RCA
18	Prospects for treatment of human African trypanosomiasis with novel diamidines: studies in the vervet monkey model of HAT.	John Thuita	TRC-KARI
19	Evidence of Central Nervous System infection in *Mastomys natalensis* infected with *T.b gambiense*.	Mwangangi	CVL
20	Biochemical changes in the advanced vervet monkey model of HAT	N. Maina	JKUAT
21	Investigations on the effects of trypanosome infection on the brain pathology and the locomotor circadian rhythm in vervet monkeys **du cer**veau et le rythme locomoteur circadien chez le singe vervet	John Kagira	IPR

N°	TITLE OF THE PRESENTATION (SUBJECT)	SPEAKER	INSTITUTION
	SESSION 5: DIAGNOSTIC		
22	Challenges and opportunities in diagnosis of African trypanosomiasis.	Joseph Ndungu	FIND
23	Specimen Bank	José Ramón Franco	WHO /OMS
24	Immunogenecity of nanobody NbAn33in the vervet monkey model	Ngotho	IPR
25	CSF responses as a means of predicting late stage HAT	Maloba	IPR
26	Monitoring Trypanocidal Drug Efficacy in Experimental Rodents Using the Loop Mediated Isothermal DNA Amplification (LAMP)	Enoch Matovu	Makerere University
	SESSION 6 : ENTOMOLOGY/EPIDEMIOLOGY		
27	Tsetse vector control: dreams of a molecular and an ecological geneticist	Johnson Ouma	TRC -Kenya
28	Salivary gland hypertrophy virus (SGHV) and endosymbiont co-infection in Kenyan tsetse populations	Wamwiri	TRC -Kenya
29	Prevalence of human infective trypanosomes in tsetse flies and HAT persistence in Western Tanzania.	Malele	TTRI
30	Population structure of *Glossina pallidipes* in Uganda and Western Kenya	Ouma	TRC -Kenya
31	Detection of *T.b. gambiense* and *T.b. rhodesiense* in domestic animals in NW Uganda	Balyeidhusa	Makerere University
32	HAT in animals perspective at Mpanda and Urambo districts in Tanzania	Mbilu	NIMR
33	Screening for Trypanosoma brucei rhodesiense in cattle and tsetse flies from Kaberamaido and Dokolo district (new focus) in NE Uganda.	Rutaro	Makerere University
34	Identification of trypanosomes isolated from humans, tsetse flies and animal reservoirs in the Trypanosoma brucei gambiense-T. b. rhodesiense interface districts of Northern Uganda.	Buhwa	Makerere University
	SESSION 7 : PUBLIC HEALTH AND SOCIO-ECONOMICS		
35	HAT management: Social and economic challenges and way forward	Salome Bukachi	Nairobi University
36	Field testing of a system to analyze routine surveillance data from the national HAT control program of the DRC	Yves Claeys	IMT-Anvers
37	Human African Trypanosomiasis: report on programs by Médecins Sans Frontières-OCBA.	Laurence Flevaud	MSF-E
38	Barriers to formal health services: Focus on sleeping sickness in Western Kenya.	Wanjala	TRC-Kenya
39	Infection rate of tsetse flies in Vwanza Game Reserve, Malawi, in June 2009.	Maganga	Mikolongwe Vet College, Malawi

in Kenya, and only two new cases have been reported in the past five years. However, despite this reduction in reported cases, the situation is still of great concern, as the program does not cover all endemic areas. The rise in the number of cases reported in CAR is due to the discovery of new foci. Uganda is the only country infested with both T.b. rhodesiense and T.b. gambiense and there is a risk that both species coexist in the same focus.

Animal African trypanosomiasis (AAT) is widespread in Tanzania and in Zambia. In Sudan, the problem exists but surveys have not been carried out due to logistics and safety issues. The vectors G. fuscipes fuscipes and G. morsitans have spread to new areas in Sudan.

The main achievements include strengthening capacities, information sharing, improvement of diagnostic tools, glossina control, and research implementation. These activities were carried out in all the countries, and were funded by international partners (WHO, AIEA, BAD, FIND, DNDi, OCEAC and others) as well as by some of the governments of the countries affected.

Current challenges include:

- Control and/or eradication of HAT

• Improve patient care

• Eliminate glossina

• Discover sensitive and specific diagnostic tools, as well as effective drugs that are accessible and easy to administer

- Improvement of control activities

• Define the populations at risk

• Update the geographical distribution of glossina in each country

• Implement WHO strategies on patient management

- Raise the necessary funds for research, control activities, and strengthening of capacities (GLP, GCP, biostatistics, ethics, etc.)

• Advocacy

• National and international support

- Build and equip sites for clinical trials and research on diagnosis

- Extend the effective implementation of NECT (Nifurtimox-Eflornithine Combination Therapy)

- Get access to all HAT foci, even during the rainy season

- Create a regional discussion forum to harmonise activities and thus avoid duplications and use funds astutely

• Promote HAT Platform – EANETT meetings

Session I was closed by the official opening ceremony, chaired by the director of KARI, who was the guest of honour.

Session 2 - Target Product Profile (TPP)

Chairman: Dr. Victor Kande, director of the national HAT control program in DRC (PNLTHA); Reporter: Dr. Augustin Kadima Ebeja, coordinator of the HAT Platform.

The Target Product Profile (TPP) was presented by Olaf Valverde, medical HAT manager at DNDi, Geneva. The TPP is very important for DNDi and for all research in drugs. The characteristics of the ideal profile, and the needs to take into consideration, include:

- Indications: which diseases?

- Population: which patient and where (specific populations: children, associated diseases)?

- Clinical efficacy: is the parasite killed, and if there is a reference drug, is the new one more effective?

- Tolerance and safety: what is the level of toxicity?

Dynamic discussions took place whose main themes are summarised below:

a) It isn't recommended to find a product active only on the hemolymphatic stage of sleeping sickness.

b) If a product developed for the neurological stage does not work, it may be worth testing whether it is active on the hemolymphatic stage. This is justified if the concentration in the central nervous system is insufficient and the product is not toxic.

c) The implementation of clinical trials on T.b rhodesiense is very difficult, and to date, there are no alternatives to melarsoprol to treat the neurological stage.

d) The ideal product should be active on both types of trypanosomes (gambiense and rhodesiense)

e) The product should be effective in all places, on all populations and age groups.

f) The treatment duration should be shorter than that of NECT.

g) Several criteria should be considered, not just one, to evaluate the benefits when choosing an acceptable profile.

h) As trypanosomiasis patients often suffer from associated diseases, the product must not have negative effects on concomitant treatments.

In conclusion, DNDi will take into account the various

contributions from the participants and suggests a profile to target research for new molecules to control sleeping sickness.

Due to a change in the programme, the MSF-Spain HAT program report planed in session seven was presented here by Laurence Flevaud.

Since 2007, MSF-Spain has worked in three countries using a different approach for each one of them:

a) In the Central African Republic (CAR): integration of HAT control in a healthcare package.

b) In the West Nile region of Uganda, in close collaboration with the national HAT control program (PNLTHA - Programme National de Lutte contre la Trypanosomiase Humaine Africaine), a vertical approach including active screening in certain communities, training, and monitoring the quality of diagnosis and treatment.

c) In Sudan, MSF-Spain is present in Western Equatoria, offering healthcare to the populations affected by the conflict. MSF works jointly with PNLTHA to exchange information and monitor trends.

The general conclusion of this report is that even though the elimination of HAT is the final objective, it isn't likely to happen soon due to difficulties in implementing complex diagnosis and treatment algorithms, a lack of research and development, and safety issues in certain regions.

Collaboration between all the actors involved in HAT is necessary, action plans designed by the countries with the help of all the actors (WHO, PNLTHA and NGOs) must be encouraged, and research activities must be maintained and increased to improve or replace the existing diagnostic tools and treatments.

Session 3. Treatment/Clinical trials

Chairman: Mbulamberi Dawson and reporter Enock Matovu

One keynote address and four papers were presented during this session.

The keynote lecture was presented by Dr. Pere Simarro, Medical Officer in charge of the WHO human African trypanosomiasis programme in Geneva, and centred on the WHO support to national policies for HAT to provide access to the best treatment available. The presentation highlighted complexities with previous drugs, including the background on initial work on combination therapy in Uganda, where it was shown that only NECT was considered worth developing (MelB/Nifurtimox, Mel B/ DFMO were highly toxic). At the start of the NECT clinical trial in 2003, 80% of patients were being treated with Mel B despite knowledge of its toxicity; only NGOs could afford to use DFMO. However, by 2009, 62% of all late stage patients were being treated with DFMO; the profile had also changed from 99% use by NGOs to over 70% by national programs. This was a great accomplishment that took 6 years and 9 months to achieve. Presently, endemic countries with 95% of affected patients regard NECT as first choice. WHO has trained health personnel to facilitate the use of DFMO as a main treatment. They engaged manufacturers sanofi-aventis and Bayer to donate and help develop the NECT kit. It was noted that even if countries do not pay for NECT, there is a cost that impacts on the WHO. More than $3.000.000 has so far been spent on distributing the kits. The importance of ongoing pharmacovigilance, where side effects linked to both DFMO and nifurtimox are reported, was also emphasised.

A paper entitled “NECT Field” was presented by Dr. Cecile Schmid from the Swiss Tropical and Public Health Institute (Swiss TPH). The need to study NECT in real situation, outside the usually strict provisions of a clinical trial, was stressed. The aim is to assess clinical response, safety (incidence of side effects) and feasibility of NECT. This is a Phase IIIb, non-controlled study that included 630 patients , of whom 16% were children and 7% pregnant/ breastfeeding mothers. The following adverse events (AEs) were observed: 92% had at least 1 AE, 12% experienced severe AEs, 5% serious AE. Most frequent were gastrointestinal (61%), fever (30%), convulsions (9%); there were few injection site reactions.. A compliance of 98% was realised, and patients spent in average 16 days at the hospital. It was reported that training is very important (catheters and infusion techniques) and that logistics are still demanding, requiring 3 shifts of staff to be in place. But the observed excellent primary efficacy was encouraging; fatality and AEs were as expected based on DFMO results.

A second paper, entitled “Tolerance and feasibility of NECT for second stage T. b. gambiense HAT in Doruma, NE DRC”, was presented by Dr. David Schrumpf from MSF-CH. The objective was to determine tolerance of NECT in all patients, including children. A retrospective analysis (Dec 2009-Jun 2010) was done describing that of the 116 patients treated with NECT, including patients under 20 WBC, no deaths during treatment were observed, while 114 (98.2%) completed treatment. There were no major AEs in children, therefore NECT appears to be safe for children. There were two relapses at 6 months follow-up. The presenter expressed his views on NECT from a doctor’s point of view. He considered the key requirement for NECT was proper nursing, and that a doctor would only be required in case of SAE, e.g. if psychosis sets in. This would necessitate a search for symptoms in order to treat the patient earlier and more aggressively. He emphasized special considerations for nausea and vomiting, that patients must be observed post nifurtimox intake. Other

recommendations included teaching nurses how to manage convulsions before calling the doctors, and preventing catheter induced reactions. It was noted that at least 8 nurses would be required for a maximum of 35 patients/day. It was recommended that all available data on NECT safety in children should be provided to WHO for analysis.

The third paper, "Fexinidazole: update on phase I clinical trial", was presented by Dr. Nathalie Strub from DNDi. This study aims to develop a safe and effective oral treatment for late stage, but also a drug that is acceptable for early stage. After completing essential studies of preclinical development (pharmacology, toxicology and pharmacokinetics), fexinidazole entered phase I clinical development in a three-part sequential study in human healthy volunteers. The study aimed to investigate the maximum tolerated dose in order to find the best dosage for an efficacy and safety study in patients with sleeping sickness. The first part of the study tested the effect of single ascending doses of fexinidazole, from 100 mg up to 3600 mg, in 9 cohorts of 8 volunteers each, 2 of whom received placebo and 6 received fexinidazole suspension. This showed a good tolerance without clinically significant adverse events even at the highest dose. In the second part of the study, the pharmacokinetics of 1200 mg of fexinidazole given either as a suspension or as tablets under fasting conditions was compared with that of fexinidazole in tablet form taken with a high fat breakfast in a crossover design. Twelve volunteers received all forms, each time followed by a washout period of 2 weeks. This comparative bioavailability study showed that the plasma level of fexinidazole was 4 times higher when given with food than under fasting conditions. Again, no meaningful adverse events were reported. The third part of the study compared repeated administration of several doses (from 1200 mg up to 3600 mg per day), during 14 days. In the group that received the highest dose, after the end of the treatment, one volunteer showed a significant and transient transaminase elevation without cholestasis or relevant clinical signs. This increase resolved spontaneously after 2 weeks and the volunteer was discharged as planned in the protocol. Further research is planned to continue the assessment of the safety profile of fexinidazole.

The last paper, "Necessity of developing pharmacovigilance (PV) activities for trypanocidal drugs in affected areas", was presented by Dr. Michel Ntama (from Unikin DRC). The background information included typical AEs such as diabetes in pentamidine treatment, melarsoprol-related encephalopathy, or typical DFMO-related gastrointestinal problems. The need to observe these AEs to maintain compliance was emphasized. It was reported that a national centre for pharmacovigilance was established with support from WHO. Its aim is to detect and identify severity and frequency as well as understand mechanisms, risk factors, consequences and prevention of AEs by instituting counter measures. PV was reportedly done by reporting cases promptly and analysing them. In a program started in 2007, personnel were trained to note down adverse events and to understand the disease/drugs in use. A focal point was trained and regular contact maintained. An awareness campaign for staff and feedback to the program was ensured. This information will be used to formulate new studies on improving drug safety (reduce AEs) and provide better treatment/patient care.

Session 4 - Drug discovery and animal models

Chairman: Dr. Maina Ngotho from JKUAT; Reporter: Dr. Gedeão Vatunga from ICCT-Angola

Four communications were presented.

Identification and mode of action of new trypanocidal molecules extracted from medicinal plants in the Central African Republic by Dr. Louise Mariette Dethoua from Institut Pasteur, Bangui, CAR. The purpose of the study was to determine the trypanocidal effect of three plants (Terminalia glaucescens, Khaya anthotheca and Pueraria javanica) used locally to treat trypanosomiasis. A phytochemical study was conducted, with in vivo tests on mice infected intraperitoneally with 5104 T.b. gambiense, as well as in vitro tests using a solution of plant extract at a concentration of 25mg/ml.

In conclusion, Pueraria javanica does not produce any trypanocidal effect, whereas Terminalia glaucescens seems to have an effect, although there were differences between in vitro and in vivo results. During the debates, participants recommended that more research be done on medicinal plants to discover new trypanocidal molecules with a more favourable efficacy/safety ratio.

Dr. JK Thuita from TRC, presented a study on HAT treatment prospects with the new diamidines, evaluating the safety and tolerance of diamidines using the vervet monkey model. At 30 mg/kg orally for 10 days, DB868 was shown to have a better safety profile than the other drugs. For CPD-0802, the IM route at 5 mg/kg for 5 days was better tolerated than the IV route. The second objective was to evaluate the efficacy of DB844 for stage 2 T.b. rhodesiense infection. DB844 was shown to have the best potential compared to pentamidine and DB289, but the other aspects of its efficacy must be evaluated as well. The efficacy of CPD-0802 and DB868 was also evaluated on stage 2 T.b. rhodesiense infection. Both showed some activity against trypanosomes in the CSF.

Effects of trypanosome infection on brain pathology as well as the locomotor and circadian rhythm in vervet monkeys, were presented by Dr. JM Kagira from the Institute of Primate Research (IPR). This study describes the brain lesions in the neurological stage of the disease using the vervet monkey model, the normal locomotor and circadian

rhythm in vervet monkeys, and the effect of trypanosome infection on this rhythm. Neuroinflammatory signs are seen in the brain: meningitis, choroiditis, ependymitis, encephalitis with lymphocytes, plasma cells, and Mott cells were observed. The pattern recorded in the circadian studies showed that the monkeys' behaviour was normal during the day, whereas beginnings of peaks and shifts in activity were seen at dawn and twilight. After the infection, a drop in total activity and daytime activity was recorded, whereas nocturnal activity was increased. These peaks and drops in daytime activity were highly variable. After the treatment and cure with melarsoprol, the behaviour returned to normal within 30 days. According to the speaker, vervet monkeys may provide a privileged model for the study of HAT, as their normal circadian rhythm is diurnal (unlike mice whose circadian rhythm is nocturnal). The author aims to determine the correlation between locomotor activity and biomarkers by filming the animals.

Biochemical changes in the vervet model of late stage HAT were presented by Dr. Ngotho Maina from JKUAT. Biochemical changes were suggested as important markers of the severity of the infection. The authors of this study wanted to examine glucose (after overnight fasting), cholesterol, triglyceride and creatinine kinase blood levels in monkeys experimentally infected with T.b. rhodesiense IPR 001. Urine analyses were also conducted to measure the pH, ketones and proteins. The speaker concluded that T.b. rhodesiense IPR 001 affects the metabolism of vervets, and causes hypoglycemia, hypertriglyceridemia, reduced HDL levels, raised creatinine kinase levels, ketonuria and proteinuria. He emphasised the necessity to study these parameters in the future as possible biomarkers of the course of the disease.

Session 5 - Diagnosis

Chairman: Dr. Johnson Ouma; Reporter: Dr. Mahamat Hamid Mahamat

Dr. Joseph Ndungu, Head of the HAT Diagnostics Programme at FIND, presented « Challenges and prospects in the diagnosis of African trypanosomiasis ». He described the organisation's specific activities in the development of tests for neglected diseases and explained the different contributions of those involved in their production, from feasibility studies to clinical trials, and finally to endorsement by the WHO Scientific and Technical Advisory Group.

The diagnosis of human trypanosomiasis has several constraints:

- The clinical signs are not specific, but can, in the case of T.b. gambiense be overcome by using CATT (Card Agglutination Test for Trypanosomiasis) as a screening tool.

- Direct microscopy is a difficult technique requiring an experienced technician due to low parasitaemia associated with T.b. gambiense infections..

- The mini-column technique is too expensive for African conditions.

- The disadvantage of a lumbar tap is that it is a painful and invasive procedure for the patient.

Prospects for the future are different for urban and rural settings. In cities, it is easy to confirm the diagnosis by microscopy, and to manage the patient's treatment. However, in peripheral centres , problems with constant energy supplies can have an impact on the use of microscopes. The proposed solution is to use a solar-powered microscope.

Various types of tests are being considered, depending on the directions research will take:

An initial research strategy on antigenic tests was started with 32 antibodies, of which 7 were identified for the production of a rapid test. Among these antibodies, 2 are specific to T.b. gambiense with 89% to 95% sensitivity. This test should be cheap (under a dollar) and easy to store, without requiring refrigeration.

A second generation of rapid tests for the diagnosis of T.b. rhodesiense will be evaluated and compared with microscopy, using markers that can be adapted for the diagnosis of other diseases, such as leishmaniasis or malaria. The advantages would be its rapidity and sensitivity using a 20-microlitre sample. Molecular methods by DNA amplification identified 4 fundamental elements specific to the parasite, and 2 specific to its DNA. The test is conducted at room temperature; it is fast and can be performed on samples sealed in tubes, thereby eliminating the risk of contamination.

A series of questions leading to the exploration of other means of diagnosis other than lumbar punctures followed this presenation. Research on biomarkers in blood, tears or any biological fluid was considered. Urine and saliva may be used for second-generation tests.

The second speaker, Dr. José Ramón Franco from the WHO, described the creation of a HAT specimen bank.

The bank includes samples of plasma, urine, blood, saliva and other specimens, as well as information on the donors. It was noted that although there is no standard for the size of such a databank, sample collection must conform to a set of rules, which can be constraining. The ideal profile of a biobank is difficult to define. For instance, to develop new diagnostic tools, a large number of samples are required,

which is not easy to achieve as HAT cases are falling. In addition, there are differences between the types of diseases based on the pathogen (T.b. gambiense or T.b. rhodesiense) which varies according to the area, and whose diagnosis requires different types of specimens. There are other constraints having to do with logistical, ethical, technical, and financial concerns. For example, logistical difficulties are mainly due to the complexity of the collection procedure and storage which must ensure that samples are kept at –70°C throughout international transport. Ethical aspects require that the protocol be authorised by the WHO legal ethics committee and the local ethics committee, as well as the national regulatory authorities. In addition, the patients donating samples must give their consent and have their anonymity guaranteed. Technical difficulties involve mainly the quality of the personnel performing the sampling in the field, who do not always implement all bioethical and biosafety procedures. Finally, the financial burden arises from expenses due to procedures carried out in the field, cold chain maintenance, and cost of transport.

The creation of this bank brought together numerous partners. The samples were collected from 14 sites in 6 countries. It is open to applicants involved in research on innovative diagnostic tools. It also provides new opportunities for exchange on research between the various actors, on training of personnel on the rules of good laboratory practices at the collection sites, and strengthening diagnostic capacities, equipment, and logistics. This biobank is the property of the WHO, and the availability of samples is determined by a WHO committee which analyses the validity of the demand. Extension to animal health is not possible as the WHO is involved primarily in human health. Procedures to authorise access to the samples must be as objective as possible, as the role of the biobank is to promote research in this disease area; the WHO is not directly involved in research only in promoting it. To guarantee the biobank's continued existence and their safety, samples are not all kept in the same location.

Session 6 - Entomology and epidemiology

Chairman: Furaha Mramba (Tanzania); Reporter: Mubarak Mustafa (Sudan)

The keynote speaker, Dr. Johnson Ouma (TRC) introduced the subject of Tsetse vector control: Dreams of a molecular and ecological genetics.

. HAT and AAT eradication failed in the past. Can we learn from this? From the 1960s, attempts at eradication of tsetse flies in different sites of Kenya, using different programmes for eradication, then he discussed about the molecular and ecological genetics on how it can contribute to the control programme, then he discussed three classes of tsetse molecular markers, the high genetics differentiation and gene flow among tsetse population and also the relation between genetics distance vs. geographic distance.

Dr. Ouma also spoke about the genetic structure and diversity of Glossina pallidipes in Uganda and western Kenya. G. pallidipes is vector of both AAT and HAT in East Africa. Recent reports indicated a big reduction of fly densities followed by a resurgence in southeastern Uganda. Western Uganda shows higher diversity. In western Kenya and southeastern Uganda populations are relatively homogeneous. These results indicated that there is a necessity of programme harmonisation between Uganda and Kenya for effective tsetse control.

Florence Wamwiri (TRC) presented Salivary Gland Hypertrophy virus (SGHV) and endosymbiont co-infection in Kenyan tsetse population. Over 500 flies from different regions of Kenya were studied, including G. pallipides, G. austeni and G. brevipalpis. Infection levels by SGHV ranged from 15 to 57%, with only 1% showing hypertrophy. G. austeni was also studied in relation to co-infection with Wolbachia (100%) and Sodalis (14%). No interference between co-infections was shown, as they were independently related.

Imna Malele (Tanzania) from the Tsetse & Trypanosomiasis Research Institute presented Human Infective Trypanosomes in Tsetse and HAT Persistence in western Tanzania. Flies were found in Katavi and Ugalla. Molecular characterisation with new tools such as PCR, SRA and LAMP was used on 897 collected flies. Both species of G. morsitans and G. pallidipes are responsible for HAT transmission but G. morsitans was found to be dominant. A high infection rate in tsetse of human infective trypanosomes is one of the reasons for the persistence of HAT in the area. Deliberate efforts need to be made to control the vector in order to break the transmission cycle through integration of various HAT control strategies

Apollo Balyeidhusa (Makerere University) talked about Detection of T. b. gambiense and T. b. rhodesiense in domestic animals in North West Uganda. The objective was to determine the significance of an animal reservoir in Gambiense sleeping sickness; pigs seem more susceptible while goats are more refractory to trypanosome infections. 417 out of 3267 samples tested positive by TBR-PCR (T. brucei) but no domestic animal in North West Uganda (NWU) was identified to be a host of T. b. gambiense trypanosomes. Results of this study suggested that domestic animals in NWU are not confirmed reservoir hosts, so humans remain the main reservoir of T. b. gambiense. No mixed infections of the two forms of HAT in NWU were noted.

Togolai Mbilu (NIMR Tabora) presented HAT in animals at Mpanda and Urambo districts in Tanzania. A higher percentage of T. brucei was noted in cattle by microscopy (10.6% in Mpanda and 4.1% in Urambo) followed by goats (2.8% in Urambo only) and in dogs only 1 out of 7 in Urambo). On FTA cards, 53.5% of cattle and 34% of goats were positive in Urambo, but only 2.1% in Mpanda.

Emmanuel Maganga, Mikolongwe Vet College, Malawi, talked about the Infection rates of tsetse flies in Vwanza Game, Reserve, Malawi in June 2009. Three different species of tsetse flies were determined, with G. pallipides and G. moristans being dominant. Infection rate was 43%. Because of high infection rates in some villages bordering Zambia, urgent combined efforts between neighboring countries is required.

Doreen Buhwa (Makerere University) presented the Identification of trypanosomes isolated from humans, tsetse flies and animal reservoirs in the Trypanosoma brucei gambiense – T. b. rhodesiense interface districts of Northern Uganda. 103 human cases and 222 animals were parasite positive in surveys from Amuru, Apach, Dokolo and Lira districts. The results suggested that T. b. gambiense and T. b. rhodesiense are still confined to distinct foci at least 100 km apart. Among the animals, 16 showed human infective T.b. rhodesiense. Entomological surveys found G. fuscipes fuscipes.

Mubarak Mustafa (Trop. Med. Res. Inst.) Khartoum, Sudan presented Risk situation for Humans - T. evansi infection in Sudan. This involved the possibility of using LAMP (PFRA and RIME) and PCR techniques in detecting T. evansi infection. No parasitological human cases were found in the study area, nor were human cases detected using LAMP technique. Positive serological PCR results of human samples indicated that there is a regular contact with T. evansi. It may be postulated that blood sucking flies can inoculate the parasites in camel herders without establishing infection.

Session 7 Public health and socio-economics

This session was chaired by Joseph Maina and Richard Lako was the Rapporteur.

The keynote speaker, Salome Buckachi from Nairobi University, presented Socio-economic and Gender considerations in Human African Trypanosomiasis (HAT) Management. She elaborated concerns regarding screening, diagnosis, treatment and follow-up.

Screening: low participation could be due to:

- the likelihood that people believe they will be tested for HIV
- the time of screening which may interfere with household work
- the distance or access to screening place
- gender of medical personnel - in some communities females are not attended by males and vice-versa
- culturally prescribed attitudes that men are strong hence they don't get sick and therefore there is no need for screening

Diagnosis: delays in diagnosis could be the result of:

- a perception that disease is caused by witchcraft
- fear, since symptoms of disease e.g. weight loss, behavior change and body weakness are often related to HIV
- a lack of symptoms, e.g. good body condition or healthy looks gives other people impression that they do not need diagnosis or treatment
- ignorance about symptoms, e.g. patient not considered to be suffering from sleeping sickness. These lead to confusion with other diseases
- gender considerations; household and social responsibilities may hinder women from going to health facilities.

Staging: lumbar punctures are:

- painful and invasive, which may discourage people from seeking treatment
- disliked because some patients are tapped in public and people will talk about them
- are avoided if the patient suffers from back pain

Treatment: problems with treatment include:

- ignorance about where the treatment can be found; perception about hospital where people go to be treated and about who needs treatment because they are going to die.
- long duration of hospitalization; patients miss out on social life or house/work activities.

Follow-up (compliance):

- perception that patient is healthy (lack of symptoms reduces chance of going back for check up); side effects

are difficult to follow up; appropriate administration; affordability of treatment; acceptability; reluctance due to disruption of social activities; poverty – poor families are affected the most.

Discussion and way forward:

- intervention needs to be appropriate to socio-economic situation

- advocacy is needed to create awareness in general population, including health workers

- privacy and confidentiality must be guaranteed (lumbar punctures must be performed in private)

- developing simplified protocol on lumbar punctures

- resources mobilisation

- look at the dynamic that affects the family and resolve related issues

Yves Claey presented on Field testing of a system to analyze routine surveillance data from the National HAT Control Program. In DRC detailed information is collected on each patient registered for treatment of HAT. However, the information recorded on paper cards does not reliably reach the provincial and national coordination levels and is not systematically analysed. As a result a major problem of resistance to Melarsoprol has gone unnoticed for years. To overcome such problems, the recording and reporting system has been strengthened and an electronic database is currently being piloted, designed to contain all patient information available from paper records. To field test the database, all patient record cards for the period 2006 -2007 were retrieved from the two provinces most affected by HAT: Bandundu and East- Kasai. Information was entered into a database; missing information was consulted in monthly reports of mobile screening units.

The research objectives were to ascertain the added value of the computerised system by assessing treatment outcomes and frequency of adverse events during this period in the two provinces. Out of 10560 HAT patients reported to have started treatment during the study period, 10,382 (2,547 from Eat Kasai and 7,835 from Bandundu) were retrieved. Information from those cards was extracted on general patient characteristics, adverse events and treatment outcome. Passive case finding was more common in Bandundu (53.3%) than in East Kasai (40.5%), yet in Bandundu 52.8% were still in stage one at the time of diagnosis as compared to 2.8% in E. Kasai. Treatment received was missing in 71.8% of cases treated in E. Kasai and 7.5% in Bandundu. Melarsoprol was the main treatment (only 0.4% treated with DFMO or NECT). Result of follow up examination could be retrieved for 33.45% of patients in Bandundu and 23.3% in E. Kasai. In both provinces, patients showing four follow up examinations were below 1%. Among 3,128 patients with at least one follow up examination, 87 (2.7%) were reported to have relapsed. Relapse rate was 0.2% in Bandundu and 13.8% in E. Kasai.

Discussion and future plans, as well as essential information on treatment prescribed is often missing and the number of patients completing the required number of four follow-up visits is almost negligible. There is no information on adverse events. There were major differences in relapse rates between the two provinces; however, in Bandundu Melarsoprol treatment appears to be effective although results can be biased because of missing information. The new database made it possible for the first time to extract information such as adverse events and relapse rate. The database can become an important instrument to monitor treatment outcome.

The presentation by Dr. Mumba Dieudonne, on Shortening post treatment follow up in gambiense Human African Trypanosomiasis described how no drug is 100% effective for treatment of HAT. At least two visits and a lumbar puncture have to be performed to show that the patient is cured. Compliance with follow-up decreases with time which contributes to increased possibility of default. The objective of the study was to shorten the duration of treatment and follow-up period, look for markers and reduce the number of follow-up examinations and lumbar punctures. Three study areas were involved from 1998 – 2008, and comparison of operation criteria for treatment outcome in T.b. gambiense were recorded. To shorten patient follow-up, WBC is the earliest and most accurate marker. Cure is defined as $\leq$5 WBC and no T.b. gambiense. Treatment failure: $\geq$ 50 WBC or presence of T.b. gambiense at 6 months. There is uncertain evolution when a count of 6 – 48 WBC are found. Criteria for test for cure at 12 months $\leq$ 20 WBC and no T.b. gambiense. Treatment failure: $>$20 WBC or presence of T.b. gambiense in any body fluid is relapse.

The presentation by Kennedy Wanjala on Barriers to formal health services; focus on sleeping sickness in Western Kenya. In Kenya, sleeping sickness is endemic in four districts bordering Uganda, namely, Busia, Bungoma, Teso and Suba. There is only one specialised health institution – the Trypanosomiasis Research Centre (TRC, formerly KETRI) – and the sleeping sickness referral hospital in Alupe which are mandated to provide health services to HAT patients. In the recent past, few sleeping sickness patients have been served at Kenya's sleeping sickness hospital. This may indicate that there is no sleeping sickness in the country or that there may be barriers within the community that

prevent sleeping sickness patients from accessing formal health services offered at the hospital. This anthropological study sought to establish whether there exist access barriers to formal sleeping sickness diagnosis. The study was undertaken in the four divisions of Teso District - Chakol, Amukura, Amagoro and Angurai. Its objectives were to (i) examine people's knowledge of and attitude to sleeping sickness, its treatment and hospitalisation; (ii) determine the factors that influence health – including behaviours of people living in the research site; and (iii) establish whether formal health agents offer referral advice to potential sleeping sickness patients. The cross sectional study used both quantitative and qualitative methods of data collection. A total of 400 respondents were interviewed, and six key informant interviews, five focus group discussions and six case studies were undertaken. The findings indicate the existence of socio-cultural barriers (stigma, ethnicity); problems with health infrastructure (poor referral services, patient – provider relations, HAT hospital identity); and geographical barriers (distance). These problems may affect utilisation of the formal health services offered at Kenya's sleeping sickness referral hospital. The study recommends development of diagnostic aid to formal health providers, including for the surrounding districts; improvement of diagnostic capability at the TRC sleeping sickness referral hospital; and continuous sensitisation of people and health providers within Teso and surrounding districts.

Current research capacities in HAT Platform countries

Prepared by Nicolas Mbongo (Congo), with the help of the representatives from other member countries of the HAT Platform. The strong points and weak points of the member countries and future prospects are summarised below.

Assets to strengthen capacities

- Presence of national policies on scientific research
- Expertise on the implementation of clinical studies (GLP and GCP)
- Operational ethics committees
- Drug regulations
- Initiatives: DNDi, FIND, EDCTP, ANDI…
- HAT Platform (5 years already!)
- Support from partners (WHO, ITMA, STPH...)

Factors hindering the strengthening of research capacities

- **Training issues**
  - Development of protocols
  - Data management (Biostatistics)
  - Regulation (drugs)
- **Maintenance of facilities**
- **Funding**

Prospects

- **Continue to strengthen the HAT Platform**
- **Set-up a funding strategy**
  - Advocacy to governments
  - Joint projects with other networks (e.g. EANETT)
- **Integration of students at the end of their studies (Master's, Doctorate) in research projects on HAT**

ON-GOING RESEARCH IN HAT MEMBER COUNTRIES		
COUNTRY	**TOPIC**	**PARTNERS**
Angola	Definition of markers for HAT staging, relapse and cure	FIND and IENT/Limoges
	Efficacy of *glossina* capture methods (traps and screens) made from fabric of various quality, colour with and without attracting agents.	OMS-TDR et l'Univ. Neuchâtel-Suisse
	Enquête anthropologique sur la THA	CRIA Lisbon; CMDT-IHMT Lisbon
DRC	NECT-Field	DNDi; Swiss TPH; PNLTHA DRC, WHO; MSF
	Documentation of bans associated with HAT treatments	IMT Antwerp
	Improvement of parasitological and molecular techniques for the diagnosis and monitoring of sleeping sickness	IMT Antwerp
	Pharmacovigilance in the provinces of East Kasai, North and South Bandundu	IMT Antwerp
	Diagnostic itinerary of HAT patients in East Kasai and Bandundu	IMT Antwerp
	Polyclonal activation of B cells in HAT: impact on acquired immunity	IMT Antwerp
	Comparison of the different fabrics used for traps and screens to control *glossina*	WHO and University of Neuchatel, Switzerland
Congo Brazzaville	Research Capacity Strengthening for Anti- trypanosomal Compounds from Medicinal Plants	WHO/TDR RCS grant 2004
CAR	Identification and mode of action of new trypanocidal molecules extracted from medicinal plants	PNLTHA/IP Bangui / Bordeaux University 2/ Montpellier University
SUDAN	Mapping of tsetse Distribution & Use of xenomontoring Techniques in Western Equatoria	TMRI/MARAF-GOSS
UGANDA	NECT	OMS/TDR
	Pentamidine	
Multicountries OUGANDA RDC CONGO SOUDAN	Développement et application des outils de xenomonitorage dans les programmes de contrôle THA dans les pays endémiques	University of Makerere, BMGF

c) Photos of the meeting (Illustration)















d) Special feature: Shortening post-treatment follow-up in patients infected with T.b. gambiense

Dr Dieudonné Mumba

Human African Trypanosomiasis (HAT), or sleeping sickness, is a lethal disease caused by *Trypanosoma brucei* (*T.b*) *gambiense* or *T.b. rhodesiense*. The management of infected patients is difficult because the treatment depends on the stage of the disease, and because two years of post-treatment follow-up are necessary before the patient can be declared cured. Several reasons have been suggested to explain why this long follow-up period is rarely adhered to.

Our objective was to shorten the duration of the post-treatment follow-up of patients infected with *T.b gambiense* based on an evaluation of the follow-up parameters and tests, and the identification of new relapse and cure criteria. Such shortening would improve patient care and would have added operational and financial advantages for the control programs. Our two-part study, one retrospective the other prospective, was carried out in the Democratic Republic of Congo, in two geographically and demographically distinct *foci*.

The detection of parasites in lymph, blood, or cerebrospinal fluid (CSF) confirms unequivocally a treatment failure or a relapse. However, the limited sensitivity of parasitological techniques slows down the diagnosis of a relapse during the follow-up. Consequently, the leukocyte count in CSF is used as an early marker of an on-going intrathecal infection or a relapse. We evaluated the different operational criteria, based on the presence of trypanosomes and the absolute or relative leukocyte count in the CSF, which were used and published to estimate the HAT treatment result. The criteria which showed the greatest accuracy in the diagnosis of a relapse was the *"presence of trypanosomes in the blood, lymph or CSF at any time during the follow-up after the treatment, and/or a leukocyte count in the CSF ≥ 50 WBC/µl as of 6 months after the treatment"*. This criteria provides a high sensitivity and specificity for the early detection of a relapse.

Few studies have been carried out on the changes in the leukocyte count in the CSF in cured patients. A sound knowledge of these changes would help confirm the patient's cure earlier than the current deadline of 24 months after treatment, and thus reduce the number of visits and avoid unnecessary lumbar taps. We created a mathematical model that describes the changes in leukocyte count in the CSF of cured patients. This parameter returns to normal in two stages: a gradual reduction in the leukocyte count in the CSF up to 12 months after the treatment, followed by a stabilisation stage where the count remains almost constant. This shows that the leukocyte count in the CSF of cured patients returns to normal 12 months after treatment.

In addition to the follow-up parameters recommended by the WHO, i.e. the presence of trypanosomes, the leukocyte count and total protein level in the CSF, we believe total IgM, specific anti-trypanosome antibodies, and interleukin-10 (IL-10) should also be tested in the CSF. We estimated their accuracy in differentiating patients with a relapse from those that are cured. The presence of parasites remains the irrefutable proof of a relapse. Among the other CSF parameters, the leukocyte count in the CSF 6 months after treatment was the best criteria to distinguish patients with a relapse from those that are cured, followed by IgM, IL-10 and total proteins at 12 months, and the specific anti-trypanosome antibodies at 18 months. The combination of leukocyte count in the CSF and IgM level, provided an accurate detection of relapse at 12 months in the retrospective study, but it provided no added value compared to the leukocyte count in the CSF alone in the prospective study.

The detection of trypanosomes and the leukocyte count in the CSF remain the reference parameters to differentiate early and accurately patients with a relapse from cured patients. Based on these two parameters, 4 algorithms were created to distinguish patients with a relapse (50 WBC/µl or presence of trypanosomes) from cured patients (£ 5 WBC/µl) during the interim control visits. Those with a relapse were treated again, whereas no further visits were necessary for cured patients. The other patients (6-49 WBC/µl) had to continue with the follow-up visits. At the cure test visit, scheduled at 6, 12, 18 or 24 months depending on the algorithm, the last remaining patients were identified as relapsed or cured on the basis of the detection of trypanosomes and leukocyte count in the CSF with a threshold at 20/µl. The algorithm with an interim follow-up at 6 months and a cure test at 12 months provide a much shorter follow-up period with fewer lumbar taps and an accurate diagnosis.

Before implementing this new follow-up algorithm on a larger scale, especially in treatment studies and in patients infected with *T.b. rhodesiense*, its accuracy will have to be evaluated on cohorts of patients, including those treated with other drugs. To improve even further the follow-up strategy described in this study, it is important to continue to evaluate other parameters associated with neuroinflammation. Of these parameters, those which will appear useful for a precise and short follow-up of patients infected with trypanosomes must be translated into a test applicable in the sites where such patients are treated and monitored after treatment.

Latest scientific events and miscellaneous information

a) Prospective of Research in Southern Sudan, by Dr. Richard Lako, MD, MSc. MOH GoSS

Southern Sudan is a impending nation emerging from more than two decades of conflict and as such health research has not been a priority. The disease burden in the country is enormous, ranging from outbreak prone disease to neglected diseases, many of which are present in southern Sudan wher routine health management information systems are largely not operational. Data or information for action is currently obtained by means of assessment, mapping exercises and surveys. The southern Sudan Government has no national body to oversee research activities, including monitoring. The amount of published literature from before the conflict is minimal and would have covered Sudan as a whole rather than focusing specifically on southern Sudan. Since the signing of the Comprehensive Peace Agreement (CPA) in 2005 there has been a huge influx of international non-governmental organizations (INGOs) into Southern Sudan, many of which focus on health. The southern Sudan Ministry of Health has also firmly established itself over the past few years, and many systems and policies have now been put in place. As a result, the procedure for carrying out health research is improved. However, given the short time period, no research policy been developed to guide research in southern Sudan and published literature still remains sparse with most information coming from internal organizational reports.

The Ministry of Health has established an ethical committee with a mandate to review all health research proposals, issue approvals and disseminate the findings to stakeholders. This committee was also trained on good practice in research through support of the HAT Platform in 2009. It has signed memoranda of understanding with institutions such as Connecting Health Research in Africa and Ireland Consortium (ChRAIC).

The ministry's road map for research in southern Sudan is summarised below;

- Develop research policy, guideline and SOP to regulate research activities in the country
- Establisha national research council
- Equip the existing research library with both electronic and hard copies of the research topics so that it becomes a resource centre for health-related topics
- Establish linkages and collaborative work with local and international research institution inside and outside the country, including the universities
- Develop website to support the research findings
- Identify research priority areas
- Conduct operational research with emphasis on neglected diseases
- Build and strengthen research capacity in country

b) Presentation of the initial NECT field results (provided during the ASTMH meeting)

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Introduction: In 2008, the pivotal Phase 3 NECT trial was successfully concluded in two African countries[1]. It showed that the Nifurtimox-Eflornithine Combination Therapy (NECT) is as effective and safe as standard eflornithine monotherapy. In March 2009, NECT was included in the 16th WHO Essential Medicines List as treatment for second-stage sleeping sickness due to T. b. gambiense. Currently, WHO is supporting its introduction as first-line treatment in endemic countries and shipping treatment kits. However, to become widely used in remote rural settings of sleeping sickness treatment facilities, logistical barriers must be overcome, healthcare staff must be trained and

well instructed. The safety and efficacy profiles under such conditions must be better known. A Phase 3b clinical trial, NECT-FIELD, is ongoing to further document the clinical tolerability, feasibility and effectiveness of the combination therapy in real-life settings, i.e. under National HAT Control Programme conditions.

The aim is to broaden the safety and efficacy information in all possible target populations including those seriously ill, children and pregnant/lactating women and strengthen the evidence base for the applicability of NECT under field conditions. For the first time, information on the treatment of these special populations has been collected. Between April 2009 and June 2010, 629 patients were recruited and treated with NECT in six sleeping sickness treatment centers and reference hospitals in the Democratic Republic of the Congo. Efficacy (discharged alive) and safety during the hospitalization period (median 16 days, including pre-treatment and post treatment observation period) are currently being analysed.

Table 1: Adverse Events	NECT-FIELD	NECT (Priotto 2009)	DFMO (Priotto 2009)
	(N=629)	(N=143)	(N=143)
Average adverse events per patient	4		5
Patients having at least one Adverse event	578 (92%)	95%	96%
Related Adverse Event	556 (88%)		
Severe Adverse Event (CTC grades 3-5)	77 (12%)	14%	29%
Serious Adverse Event (SAE)	32 (5.1%)	0.7%	4%
Fatalities	10 (1.6%)	0.6%	2.1%
Treatment cessations	5 (0.8%)	1.4%	8%

Objectives: The primary objective was to assess the clinical response of the NECT co-administration under field conditions. The secondary objectives were to assess the incidence and type of adverse events , and the capacity of the treatment centers to deal with these; to assess the feasibility of the implementation of the NECT co-administration by the health centre; and to assess the effectiveness of the NECT co-administration at 24 months after treatment.

Inclusion Criteria: All patients with T. b. gambiense human African trypanosomiasis (HAT) in the meningo-encephalitic phase; able to take the treatment, all ages, including all children under 12 years of age; male and female, including pregnant and lactating women; who signed informed consent or assented (children and analphabets) together with a responsible person or witness signature.

Study Design: Multicentre, open label, uncontrolled Phase IIIb study; sample size: 620 patients; co-administration of nifurtimox (10 days at 15mg/kg/ t.i.d.) oral plus injectable eflornithine (7 days at 400 mg/kg b.i.d) in two hours infusion.

Results: Primary efficacy response (at discharge)

A total of 629 patients received at least 1 dose of the study drug, 10 (1.6%) patients died during their hospital stay period and 619 were discharged alive (98.4%).

Safety results (in-hospitalisation): Cause of **death** was shock (1 septic, 1 cardiogenic), coma (2), anaemia (1), respiratory infection (1), general deterioration (1) and sudden death (1). 2 were not identified. 8 were considered possibly related.

SAE: 32 patients (5.1%) had 39 serious adverse events (including above death cases) among which the most frequent were: 9 neurological [coma, seizures], 4 psychiatric, 10 infectious [5 of them respiratory, 2 digestive], 3 anaemia, 3 cardiovascular). 20 SAEs were possibly treatment related, 6 probably, 6 non related to NECT 2 SAE happened in children 1 in pregnant and 3 in lactating women

Table 2: Most Common Adverse Events per special study groups and body system	All (N=629) %	Children (N=100) %	Pregnant/ Lactating (N=47) %	Other patients (N=482) %
Gastro-intestinal	**61**	**43**	**74**	**64**
Vomiting	43	31	63	44
Nausea	20	13	11	22
General disorders	**46**	**57**	**70**	**42**
Fever	30	44	39	26
Asthenia	18	13	37	17
Nervous system	**34**	**21**	**33**	**37**
Headache	14	8	17	16
Vertigo	10	0	9	13
Convulsions	9	10	7	9
Metabolic	**26**	**22**	**17**	**28**
Anorexia	25	21	15	27
Psychiatric	**16**	**9**	**9**	**18**
Agitation	6	5	9	6
Insomnia	6	3	0	8
Musculoskeletal (pain)	**14**	**4**	**17**	**15**
Respiratory	**10**	**7**	**9**	**11**
Skin disorders	**9**	**9**	**7**	**10**
Pruritus	7	6	7	7

Conclusions: The safety profile of NECT, shown in previously published findings [1], was similar and no major or unexpected safety concerns arose considering the large inclusion criteria, including very sick patients. NECT became the preferred treatment against stage 2 sleeping sickness for the health care staff and the patients. The treatment is logistically demanding but feasible. It can be implemented and rolled-out to remote, rural hospitals or treatment centers.

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Participants Workshop on the validation of the guiding principles, november 2010, Kinshasa DRC,

c) Workshop on the validation of the guiding principles on the ethical evaluation of research involving human subjects in the Democratic Republic of Congo

The HAT Platform, in collaboration with CIBAF (Centre Interdisciplinaire de Bioethique pour l'Afrique Francophone) and the national HAT control program in DRC (PNLTHA), organised a two-day workshop on November 13-14, 2010 in Kinshasa, DRC, on the validation of the guiding principles of the ethical evaluation of research involving human subjects in DRC. A document was drawn up by the team set-up in April 2010.

The three ministries involved with research (Ministry of Public Health, Ministry of Scientific Research and Ministry of Higher Education and Universities) were represented by general secretaries, professors of the Public Health School, and presidents or members of ethics committees. Several other experts joined the workshop, which lead to the adoption of the document, once a few amendments were added. The HAT Platform will ensure this important tool is widely circulated.

d) Websites of interest

http://pilot.globalhealthtrials.org/

This web site curently in pilot phase, is being developed by a collaboration between many research organisations that work in the field of global health. It is open access and free. The ethos of this initiative is that those working on trials in resource limited setting can access each other; whatever their role and whatever disease they work on. Researchers can then work together to share guidance, tools and resources in order to improve trials and make them easier to conduct, thereby helping address questions around diseases of poverty. This site also provides guidance material, standard documents and training resources. There is a strong focus on careers and training with a free and comprehensive continuing professional development scheme.

2011 scientific meeting programme

Scientific event/congress	Date	Location
KEMRI Annual Scientific and Health Conference, Theme: Advances in Health Research Towards Kenya Vision 2030	9-11 February 2011.	AT KEMRI HQs in Nairobi, Kenya
East African Health and Scientific Conference organized by the College of Health Sciences, University of nairobi, Theme: Towards Optimum Health Care;	15-17 June 2011.	Kenyatta National Hospital Campus, Nairobi, Kenya
Congrès sur les Sciences de la Santé en Afrique	A confirmer	Université Walter Sisulu ; Afrique du Sud
First International Society for Infectious Diseases Neglected Tropical Diseases Meeting (ISID-NTD	July 8-10, 2011	Boston, USA
International Scientific Council for Trypanosomiasis Research and Control – (ISCTRC)	Sept 2011 Dates TBC	Bamako, Mali
7th European Congress on Tropical Medicine & International Hygiene (FESTMIH).	Oct 3-6, 2011	Barcelona, Spain
Infectious Diseases Society of America 49th Annual Meeting (IDSA)	20-23 Oct, 2011	Boston, USA
Joint Annual conference of the Japan Society of Tropical Medicine and the Japan Association for International Health (JSTM/JAIH)	4-6 Nov, 2011	Tokyo, Japan
American Society of Tropical medicine and Hygiene, 60th Annual Meeting (ASTMH)	Dec 4-8, 2011	Philadelphia USA

Facilitators Workshop on the validation of the guiding principles, Kinshasa, DRC

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